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A Biographical Memoir by

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Robert G. Edenfield

ROBERT COOLEY ELDERFIELD

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BY NELSON J. LEONARD

ROBERT C. ELDERFIELD WAS an organic chemist who achieved considerable success in applying his research to areas of medicine. While at the Rockefeller Institute for Medical Research, he established the fundamental relationship between the cardiac aglycones and the sterols and bile acids. He determined the stereochemical structures of the rare sugar components of the related glycosides. Together with his students at Columbia University and later at the University of Michigan, he worked on alkaloids, provided the best synthetic routes to the effective antimalarial pamaquine, examined a new category of anionic substitution reactions, and contributed to our array of anticancer agents. His breadth of research contributions was complemented by his enthusiastic and innovative teaching and by his writing. He was editor and author of the nine-volume definitive treatise *Heterocyclic Compounds*.

Robert Elderfield was born May 30, 1904, in Niagara Falls, New York, the son of Charles James Elderfield and Nellie Cooley. Charles's parents were Ellen Croal of Aberdeen, Scotland, and Charles Elderfield of the Isle of Wight, England. Robert's grandfather was a skilled cabinetmaker who, with Ellen, emigrated to Hamilton, Ontario, and from there

moved to Niagara Falls, New York. Robert's father dropped out of school at the age of fourteen to help support the family by employment at Oliver Brothers in Niagara Falls. There he met and married Nellie Cooley in 1901. Born in Canandaigua, New York, she attended Upham School for Girls to learn secretarial skills and found a job with the same employer. Charles J. Elderfield went on to found and become president of a prosperous mill supply business. He was, incidentally, an enthusiastic fisherman, and he transmitted this passion to his son, Robert, who from the age of four spent part of every summer fishing in Canada, except during the war years. There will be more said about the son's fishing prowess later.

Robert Elderfield's early years were spent in attendance at the public schools of Niagara Falls. Inasmuch as he was rather young when he finished high school in 1920, he was advised to attend a preparatory school prior to entering college. The Choate School in Wallingford, Connecticut, was selected. His original plan was to go directly thereafter to the Massachusetts Institute of Technology for undergraduate work, but upon the advice of his cousin Mortimer E. Cooley, Dean of the Engineering School of the University of Michigan, Robert decided to attend a small liberal arts college, Williams College, before going to MIT for graduate work. To satisfy the entrance requirements for Williams, particularly insofar as Latin was concerned, he returned to Choate for a second year, completing that requirement and accumulating considerable advanced credit. While he was at Choate, his parents adopted a girl of eight years, Esther, whose mother had died in the flu epidemic of 1918. Robert realized that his new sister was confused and unhappy, and for her first Christmas in the Elderfield family he gave her a black Labrador puppy. This was followed by gifts of a sled, ice skates, and skis as further evidence of his caring and

understanding, all of which is still remembered warmly by Esther (Sherwood Elderfield Green).

At Williams, Robert majored in chemistry and qualified for a second major in German, which gave him a great deal of satisfaction. During his senior year at Williams, he was a teaching assistant in the freshman chemistry laboratory. He received the A.B. degree in 1926. There was never a doubt that he would enter the chemical profession. During his formative years, he came in contact with many technically trained individuals who were connected with the chemical industry that was then concentrated in the Niagara Falls region. During the summers between his college years at Williams, he worked in chemical plants in Niagara Falls. The experience thus gained strengthened his desire to pursue a career in chemistry.

The first research paper that bore the name of Robert C. Elderfield appeared with that of MIT Professor Tenney L. Davis in 1928. The Ph.D. degree was awarded by MIT in 1930, and in 1932 and 1933 Elderfield and Davis published two more papers that were based on his thesis research. An important development of his MIT years resulted from his appointment as a laboratory assistant. One of the students in the undergraduate course to which he was assigned was Mary Elizabeth (Polly) Betts, who had been born in Philadelphia and brought up in Washington, D.C. Robert and Polly were married in the summer of 1930. She died only recently in February of 1999. Their two daughters survive: Nancy Elderfield Hall Shanahan and Margaret Helen Elderfield Ritchie.

Appointed assistant in 1930 in the Rockefeller Institute of Medical Research, Elderfield worked with Walter A. Jacobs in the Laboratory of Chemical Pharmacology. The research was concentrated on the cardiac glycosides, a category of natural products noted and used for their specific action

on the myocardium. Little was known initially about these compounds, which are present in plants in extremely small amounts. One of the major goals of the research was to determine any structural interrelations that might exist, and one of the strategies was to concentrate on those sources (e.g., *Strophanthus kombé*) wherein the glycosides were most abundant. It should be remembered that in the 1930s the methods of comparison of compounds were limited mainly to ultraviolet spectroscopy and to identity in physical properties. The structural achievements of the era were remarkable in the light of these restrictions, together with the lack of efficient methods for separation of the mixtures of compounds that nature provided and the small number of degradation procedures available. The twentieth article in the Rockefeller series on strophanthin was the first to include Elderfield's name as an author, and the thirty-fifth article in the series was the last. By means of conversions and degradations, strophanthidin was correlated with periplogenin and these two were correlated to digitoxigenin and gitoxigenin. The Rockefeller studies merged with research that had been going on in Germany to show that the cardiac aglycones were closely related to cholesterol and the bile acids, an important conclusion that had not been foreseen. Elderfield related in his *Biographical Memoir* of Walter A. Jacobs (vol. 51, National Academy Press, 1980) the amusing account of the successful degradation of a digitoxigenin derivative to etiocholanic acid for structural correlation. Elderfield committed their entire supply, a few hundred milligrams, to a process that took three days and nights, while Jacobs, who had been hesitant to commit the precious substance to such a series of reactions, was out admiring the fall foliage in the Adirondack Mountains. Elderfield's own work at Rockefeller was also responsible for determi-

nation of the structure of the rare sugar cymarose and its relationship to digitalose.

In 1936 Elderfield moved to Columbia University, where he was an assistant professor for only one year, associate professor during 1937-41, and professor of chemistry (1941-52). There he taught a comprehensive lecture course in organic synthesis that for the first time stressed intermediates, reaction pathways, and relative costs of different routes to the desired products. His laboratory course in advanced organic synthesis was no less rigorous. During my graduate time at Columbia (1939-42) he showed us that he was indeed a terrific experimentalist. Once, when I was having trouble purifying reaction intermediates, he zipped through a four-step sequence on a one-mole scale during two evening sessions. Center cuts of the liquids had perfect elemental analyses, and the initial and terminal refractive indexes of each lot were uniform. I learned by watching and assisting, and I was most grateful for his guidance.

While Elderfield's individual research directions and advice to his graduate students involved a scientific jargon that combined tough vernacular, slang, and metaphor, he gave that advice freely and was always available. He showed great compassion and helped more than one student who got in trouble. He was also supportive of the graduate student society that was organized in my time at Columbia. A fair number of our classmates were "subway graduate students" who had no place to relax or study between classes. A graduate student lounge was the answer. Elderfield and the other faculty members provided funds to convert a classroom (gift of Columbia) for use as a lounge and group seminar room.

Elderfield's humor ran to teasing, an observation corroborated in communication with members of his family. He helped organize an expedition that took advantage of

some of the city-dwelling students by taking them on a "snipe hunt" on a moonless night. We left the "baggers" widely distributed in a park in Westchester County while we "beaters" retired to an all-night cafe nearby until we felt it was time to rescue them. I have been told that, when on a fishing expedition with a colleague or grandson, Bob Elderfield would usually throw back the first fish he caught, no matter the size. This bold act was usually accompanied by the statement "too small" or "grow up," which never failed to impress.

Elderfield's research at Columbia University included the subject of alkaloids with which he had become familiar while at Rockefeller University. His investigation of the cardiac aglycones was extended to include final structure verification and synthesis of model unsaturated lactones related to the aglycones. He and his students devised general methods whereby representative members of the group of cardiac drugs became available synthetically by transformations of naturally occurring sterol derivatives. The methodology, which has been widely applied, is also applicable to the synthesis of isotopically labeled compounds in the series. The pharmacological activity of representative lactones and aglycones was determined in collaboration with K. K. Chen at Eli Lilly and Company in Indianapolis, Indiana. During the years of the Second World War, Elderfield had increased responsibility. He was a section member of the National Defense Research Committee and worked on explosives. He was also executive secretary and eastern regional director of the Panel on Synthesis of the Board for Coordination of Malarial Studies (1943-46), which was succeeded after the war by the Malaria Study Section of the National Institutes of Health (1946-49), and Elderfield served as a consultant during this period. In the Columbia laboratory, he and his coworkers concentrated on the synthesis of

aminoquinoline drug candidates, discovered a previously undetected rearrangement in one of the synthetic processes, and developed several drugs that represented distinct improvements over those available for the treatment of relapsing vivax malaria. The synthetic innovation that led to the efficient production of pure primaquine (pamaquine, or plasmoquine) was the catalytic reductive condensation of 6-methoxy-8-aminoquinoline with 1-diethylaminopentan-4-one. The naphthoate salt has been used for administration to patients. During this period of antimalarial research, Elderfield enjoyed the valuable cooperation of Leon H. Schmidt of Christ Hospital, Cincinnati, Ohio, in the pharmacological work and of A. S. Alving of the University of Chicago in the clinical work of advancing the medical investigation of antimalarial therapy.

Elderfield was called to the University of Michigan as professor of chemistry in 1952, where he continued his fruitful research, writing, and teaching in a very friendly atmosphere. He did further research on antimalarials and on *Alstonia* alkaloids, structure and synthesis, and added volumes to his *Heterocyclic Compounds.* He was not only the editor of all nine volumes but he was also the author of extensive sections in each. The writing in this series reflects the breadth of his knowledge and interest, concomitant with his clarity of presentation. With his Michigan students he initiated research on novel anionic aromatic substitution reactions and engaged in an ambitious program on potential anticancer agents. The program was centered on the synthesis and testing of nitrogen mustard moieties attached to nuclei of known pharmacological compatibility. The idea was original and provocative and has certainly been stimulating to chemists endeavoring to provide multiple agents capable of attacking cancer cells. From 1952 Elderfield was a scientific con-

sultant to the (then) Sloan-Kettering Institute for Cancer Research.

At various times he was consultant for Eli Lilly and Company and Esso Research and Engineering. His awards include the Presidential Certificate of Merit (1948), election to membership in the National Academy of Sciences (1949), an honorary doctorate from Williams College (1952), and the Distinguished Faculty Achievement Award of the University of Michigan (1969). His editorial time, notable for the *Heterocyclic Compounds* series, was also donated generously to the major publications of the American Chemical Society. The memorial resolution for Professor Elderfield from the faculty of the College of Literature, Science, and the Arts of the University of Michigan (1980) included a section on his importance to his colleagues:

> As well as a superb scholar, Professor Elderfield was a tower of academic and personal strength for his colleagues, particularly the younger ones, and many of the now older members of faculty remember his support with gratitude.

Whatever he did, Bob Elderfield did well. That was simply central to his philosophy. The practice extended to building things, whether bookcases, tables, rock walls, a child's set of wooden alphabet letters, or a cabin and a cookhouse on an island in Sand Lake, Jones Falls, Ontario. He was dependable enough as a fisherman to provide breakfast or supper as needed when the family was in Canada. His pleasure in cooking ranged from making sugar cookies and doughnuts for his girls, through fish chowder and camp stew in the summer, to outdoor grilling for his students and coworkers that followed some competitive athletic endeavor in Hastings-on-Hudson while he was at Columbia. Bob's competitive enthusiasm made its appearance in Michigan when he encouraged the football or basketball team or the slow-

running horse of one of his colleagues who had decided to go into horse breeding. He and his wife, Polly, played cribbage regularly and kept annual score. Bob took great pride in the accomplishments of his students—graduates, undergraduates, and postdoctorates—and never forgot that students are an important product of university research.

I AM MOST GRATEFUL to Bob's family—his daughters, Nancy and Margaret Helen, and his sister, Esther—and to Bob's Michigan colleagues, especially Martin Stiles, for the information they provided. I also used the material that Bob himself placed on file in the Office of the Home Secretary of the National Academy of Sciences.

SELECTED BIBLIOGRAPHY

1928

With T. L. Davis. The catalytic preparation of methylamine from methyl alcohol and ammonia. *J. Am. Chem. Soc.* 50:1786-89.

1931

With W. A. Jacobs. Strophanthin. XXI. The correlation of strophanthidin and periplogenin. *J. Biol. Chem.* 91:625-28.

With W. A. Jacobs. Strophanthin. XXII. The correlation of strophanthidin and periplogenin with digitoxigenin and gitoxigenin. *J. Biol. Chem.* 92:313-21.

1935

With W. A. Jacobs. The structure of the cardiac aglycones. *J. Biol. Chem.* 108:497-513.

The chemistry of the cardiac glycosides. *Chem. Rev.* 17:187-249.

The structure and configuration of cymarose. *J. Biol. Chem.* 111:527-35.

1941

With J. Fried. Studies on lactones related to the cardiac aglycones. V. Synthesis of 5-alkyl-α-pyrones. *J. Org. Chem.* 6:566-76.

1943

With E. R. Blout. Synthesis of β-substituted-$\Delta^{\alpha,\beta}$-butenolides from methyl ketones. *J. Org. Chem.* 8:29-36.

1947

With F. C. Uhle and J. Fried. Synthesis of glucosides of digitoxigenin, digoxigenin and periplogenin. *J. Am. Chem. Soc.* 69:2235-36.

1948

With F. J. Kreysa, J. H. Dunn, and D. D. Humphreys. A study of the synthesis of plasmochin by the reductive amination method with Raney nickel. *J. Am. Chem. Soc.* 70:40-44.

1950

Three-, four-, five-, and six-membered monocyclic compounds containing one O, N, and S atom. In *Heterocyclic Compounds*, vol. 1. New York: John Wiley & Sons.

1952

Certain anionic aromatic substitution reactions. *Rec. Chem. Prog.* 13:119-128.

With E. Werble. 6-Methoxy-8-(4-amino-1-methylbutylamino)quinoline, U.S. Patent 2,604,474, July 22.

1954

With S. L. White. *Alstonia* alkaloids (IV). The structure of alstoniline. *J. Org. Chem.* 19:683-92.

1957

With H. E. Boaz and E. Schenker. *Alstonia* alkaloids (VII). The structure of alstonidine. *J. Am. Pharm. Soc.* 46:510-11.

1958

With B. A. Fischer. Total synthesis of alstonilinol. *J. Org. Chem.* 23:332.

With I.S. Covey et al. Potential anticancer agents (I) Nitrogen mustards derived from p-[N,N-bis (2-chloroethyl)amino] benzaldehyde. *J. Org. Chem.* 23:1749-53.

1960

With T. H. Bembry and G. L. Krueger. Amino derivatives of strophanthidin (I) Reaction of primary and secondary amines with the butenolide side chain of strophanthidin. *J. Org. Chem.* 25:1175-79.

With E. LeVon. Potential anticancer agents (III) Nitrogen mustards derived from 8-aminoquinolines. *J. Org. Chem.* 25:1576-83.

1961

With T.-K. Liao. Potential anticancer agents (XII) Nitrogen mustards from p- aminobenzoic acid derivatives. *J. Org. Chem.* 26:4996-97.

1967

Pteridines, alloxazines and compounds with 7- membered or larger rings. In *Heterocyclic Compounds*, vol. 9. New York: John Wiley & Sons.

With J. Roy. Synthesis of potential anticancer agents. XVIII. Nitrogen mustards from 6-substituted coumarins. *J. Med. Chem.* 10:918-21.

With A. C. Mehta. Synthesis of potential anticancer agents. XIX. Nitrogen mustards from 7-hydroxycoumarin derivatives. *J. Med. Chem.* 10:921-23.

1969

With J. M. Cook and P. W. Le Quesne. Alstonerine, a new alkaloid from *Alstonia muelleriana*. *J. Chem. Soc. D.* 1306-1307.

1972

With R. E. Gilman. *Alstonia* alkaloids. XI. Alkaloids of *Alstonia muelleriana*. *Phytochemistry*. 11:339-43.