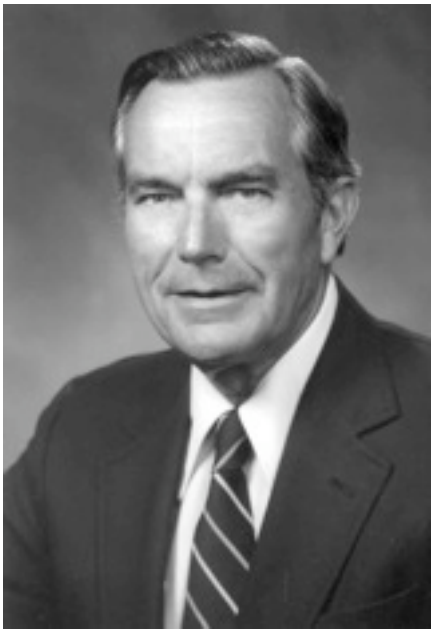

Nelson J. Leonard

September 1, 1916 – October 9, 2006

The passing of Nelson Jordan Leonard on October 9, 2006 at age 90 deprived us of a chemist who produced highly significant research and possessed those human qualities that led to a wide personal popularity. Leonard was a primary contributor to fundamental knowledge of the chemistry of nitrogen-containing organic molecules. The sweep of his research covered alkaloids, nitrogen heterocycles, small- and medium-ring compounds, transannular interactions and reactions, natural and synthetic cytokinins that facilitate cell growth, cell division and cell differentiation, chemical, spatial, fluorescent and dimensional probes of enzyme-coenzyme interactions and of nucleic acid structure and function and fluorescent covalently-linked DNA/RNA cross sections of normal, narrow and wide dimensions. He was a master in the application of organic synthesis to the solution of important problems in biochemistry and plant physiology.

Nelson Leonard joined Organic Syntheses Inc. as a member of the Board of Editors in 1951 and was the Editor of Vol. 36 published in 1957. He served on the Board of Directors (1969-2001), as Vice President (1978-1980) and President (1980-1988). In gratitude for his service, Organic Syntheses, Inc. provided funds to assist in the endowment of the Nelson J. Leonard Distinguished Lectureship at the University of Illinois and sponsors the Nelson J. Leonard Graduate Fellowship administered by the ACS Division of Organic Chemistry.

Shortly before his death, Nelson completed and published his autobiography entitled *More Than a Memoir* (ISBN 1-59926-791-8). In addition to this book, Nelson left an extensive document recalling in his own view the most significant personal and professional events, influences and achievements of his life's journey. This article is largely based on that document.

Nelson was born on September 1, 1916, in Newark, New Jersey, to Harvey Nelson Leonard and Olga Pauline Jordan. His father's ancestors had come from England in the first half of the seventeenth century while his mother's forebears were Huguenots who left France for Germany in the sixteenth century and sailed to the United State in the mid-nineteenth century. Both parents' families followed a puritan work ethic that was

relieved by music (piano, organ, mandolin and singing) and an appreciation of nature (hiking, swimming, etc.). Nelson's father was a salesman of men's clothing and he developed a large and loyal following of customers who transferred allegiance from store to store in New York City whenever he shifted employers.

Nelson attended public schools in Mount Vernon, New York. In high school Nelson was active in student politics, in the glee club, in the presentation of operettas and in solo recitals. His graduation year 1933 was in the trough of the depression. Political storm clouds were gathering over Europe with the accession of Hitler to power and, in the United States, the banks were closed. When the Mount Vernon bank in which Nelson had deposited his hard-earned savings was allowed to reopen, he had half enough money for a first year in college. His matriculation to Lehigh University in Bethlehem, Pennsylvania, was made possible by a scholarship. He played varsity soccer, was class president in his junior year, was active in theater and operetta productions, in glee club concerts and in radio appearances. An intended chemical engineer through his junior year, he shifted to a B.S. in chemistry curriculum. As a senior in 1937 at Lehigh University and in anticipation of his study as a Rhodes Scholar at Oxford, Nelson had prepared a summary of the scientific papers of Neville Sidgwick and had been fascinated by Sidgwick's *Organic Chemistry of Nitrogen*. This interest proved to be quite anticipatory of Nelson's later research on nitrogen compounds. While at Oxford, Nelson's continuing interest in music was evident in his participation in the Oxford Bach Choir, the Opera Club, and the Lincoln College Choir. His sport shifted to rowing.

The beginning of World War II in September 1939, forced Nelson's return to the United States and the termination of his research with Leslie Sutton on the use of fluoro compounds in the determination of valency angles by electric dipole moment measurements. Chemistry was not the only part of Nelson's life that was interrupted by the war. Through family connections, he had met and fallen in love with Louise Cornelie Vermey of the Netherlands. After a year and a half, they became engaged but were not to see each other again until the end of the war, 1945 (in Holland) and were not able to arrange for her journey to the U.S. and marriage until 1947.

Nelson was able to continue his graduate education in chemistry, concluding with a Ph.D. (1942) at Columbia University, New York. His research, which consisted of structure establishment and partial synthesis of alstonine, a naturally occurring antimalarial, was done under the direction of Robert C. Elderfield.

A postdoctoral research assistantship brought Nelson to the University of Illinois, Urbana-Champaign, where he worked with Roger Adams on *Senecio* alkaloids. Teaching duties were added in 1943, which grew to include U.S. Navy and U. S. Army units passing through the University of Illinois. He joined the team of Charles C. Price, III, and Harold R. Snyder on antimalarial research to help with the synthesis and production of chloroquine in time for its use in the Pacific. At the end of the war, during 1945-1946, Nelson served as a Scientific Consultant and Special Investigator to the Field Intelligence Agency Technical, U.S. Army and U.S. Department of Commerce, European Theater. He returned to the University of Illinois and remained on the teaching staff until his retirement in 1986, by which time he was Reynold C. Fuson Professor of Chemistry, Professor of Biochemistry and Member of the Center for Advanced Study.

Very early in his research career, he adopted as a guiding concept, *organic synthesis with a purpose*. To this end, he developed a catalytic reductive cyclization of intermediates that led directly to *Senecio* and *Lupin* alkaloid components and establishment of their relative configurations. Synthesis of selected 1,2-diketones established the dependence of their spectroscopic properties upon the dihedral angle between the carbonyl groups. Fundamental study of the electrolytic reduction of aminoketones provided a new route to medium-ring compounds containing nitrogen. New functionalities were invented based upon transannular reactions across medium rings, which included defining the ring-size and the electronic limitation of transannular interactions. He became well known for his recognition of the iminium group (the product of enamine protonation) as a fast-acting ionic carbonyl equivalent and for assembly of new families of reactions based upon this functional group. By reaction of iminium salts with diazomethane Nelson and his students made stable aziridinium salts available. These three-membered ring compounds, postulated previously to be unstable intermediates, were investigated systematically.

From 1943 until 1955, Nelson's musical career had flourished in the Midwest along with his academic career in chemistry. Solo appearances as a bass-baritone in choral works with the Chicago, Cleveland and St. Louis Symphony Orchestras, in Bach festivals, at other universities and with many different choruses were interspersed with recitals at the University of Illinois, Washington University, St. Louis, and Illinois Wesleyan, Springfield. When, in 1955 at age thirty-eight, Nelson was elected to membership in the National Academy of Sciences, he felt that, if his peers had chosen to recognize him as a chemist, then he had better do something about it. He realized that there was more scope for originality in full-time devotion to chemistry and a more lasting contribution through the literature of science. The heavy professional demands of chemistry meant that there were no more singing performances. He and Louise (affectionately known as Nell) had four children by that time: Kenneth Jan, Marcia Louise, James Nelson, and David Anthony. Another decision point was reached in 1960, when Nelson was on sabbatical leave, aided by a Guggenheim Fellowship, in Basel, Switzerland. He had concluded that organic chemistry, *per se*, was not enough, a dictum that he passed along to his students thereafter, and he devoted much more of his time to reading the current literature of biochemistry. The broadening of his interests soon appeared in research publications emanating from the Illinois laboratory and as well as those of the scientists with whom he collaborated.
By synthesis of the cytokinin, $\underline{N}^6$-isopentenyladenine, and collaboration with Folke Skoog, plant physiologist at the University of Wisconsin, it was found that this compound occurred naturally in the plant pathogen *Corynebacterium fascians* as a major component responsible for its biological activity. The combined Illinois-Wisconsin search for other natural cell-growth, cell-differentiation factors uncovered eight additional highly active substances from plant, animal, bacterial, and fungal sources. Stereoselective syntheses to produce these compounds, and their structure/activity investigations led to agents more active than the naturally occurring cytokinins. In very low concentrations, the cytokinins initiate plant, flower, and tree growth from tissue culture that is basic to horticultural and agricultural developments. This collaboration lasted eighteen years and resulted in some fifty publications.

Leonard's laboratory provided fundamental findings on the reaction of diethyl pyrocarbonate (DEP) with adenosine and adenosine-containing nucleotides and dinucleoside phosphates, culminating in 1973 with the proposition that DEP, as a

chemical probe, could serve the purpose of detecting adenosine or deeoxyadenosine modification at exposed sites in RNA or DNA.

Concomitant with the research on triacanthine (3-isopentenyladenine) and the related cytokinins, research on spatial probes of enzyme-coenzyme interactions was initiated with the synthesis of 3-isoadenosine and its phosphates. Leonard and coworkers, with the collaboration of other laboratories, showed that the range of similar biological activities for the 3-isoadenylates with the adenylates (9-substituted on purine), while initially surprising, turned out to be readily understandable in spatial terms. Thus, the superposition of the purine ring of a 3-isoadenosine derivative over that of adenosine illustrates the close spatial relationship that exists between the two, especially the proximate location of the individual nitrogens in each. A definitive study at Illinois (1996) confirmed the hydrogen-bonding pattern that had been postulated thirty years earlier and helped in the understanding of the parameters limiting early nucleic acid development in nature. Nelson deduced that nature might have discarded the N3 (vs. N9) attachment site for purines because of chemical instability, but not of structural incompatibility.

Leonard's derivatization of nucleosides, nucleotides, and coenzymes by fluorescent probes, placed him among the most often quoted scientists. He was successful in providing reagents for 4-thiouridine, cytidine, adenosine, and guanosine. In a fruitful collaboration with Illinois biochemist Gregorio Weber, incorporation of fluorescence moieties into the related coenzymes provided details as to both size and locus of enzyme-coenzyme binding sites. The idea involved testing of the dimensional restrictions of enzyme-active sites by using synthesis to stretch the cofactor by known magnitudes.

His final forays into the synthesis of nitrogen heterocycles included the synthesis, chemical behavior, and valence orbital structure of tri-s-triazine and 1,2,4,6-tetraazapentalene. The first of these is a fundamental nitrogen aromatic ring system consisting of a coplanar arrangement of three fused s-triazine rings, with a 2π-electron periphery. This long-sought nucleus, first conceived in correct formulation by Pauling and Sturdevant in 1937, finally became available in a remarkably abbreviated synthesis.

All tolled Nelson published 438 papers and his roster of coworkers included 120 Ph.D. students and 90 postdoctorates.

Following his retirement from the University of Illinois, in 1987, Nell passed away and before long Nelson underwent serious cancer surgery himself. After recovery, he became a Fogarty Scholar-in-Residence at the National Institutes of Health, Bethesda, Maryland (1989-1990) in association with Arnold Brossi. This was followed by an appointment as Distinguished Visiting Professor at the University of California, San Diego, under the auspices of D. R. Kearns and M. Goodman and, in 1991, as a Sherman Fairchild Distinguished Scholar in the Division of Chemistry and Chemical Engineering at the California Institute of Technology, Pasadena, where he was retained as a Faculty Associate starting in 1992. He had earlier connections with Caltech through collaborations with J. D. Roberts, which originated on mutual ski vacations and resulted in four joint publications. A particularly meaningful collaboration with Jack Roberts and his wife, Edith, however, had its roots in their introducing him to Margaret Taylor Phelps, which resulted in Nelson and Peggy's marriage in 1992. Peggy Phelps introduced him, in his California years, to the world of contemporary art and to travels

centered on art and architecture and shared with Nelson an avid interest in skiing. Nelson remained involved in the musical world serving on the board of the Pasadena Symphony whose piano chair was endowed in his honor by family and friends on the occasion of his 85th birthday.

During the course of Nelson's career, he served at a consultant for Phillips Petroleum Company, Monsanto Chemical Company, Eli Lilly and Company, in that order. He lectured widely, nationally and internationally. In addition to his membership in the National Academy of Science (1955), he became a fellow of the American Academy of Arts and Sciences in 1961. He was elected a Member of the American Philosophical Society in 1996. He received the ACS Award for Creative Work in Synthetic Organic Chemistry in 1963, the Medal of the Synthetic Organic Chemical Manufacturers Association in 1970 and the ACS Roger Adams Award in Organic Chemistry in 1981. Awards continued after Nelson's retirement, including the George W. Wheland Award of the University of Chicago (1991), the (first) Creativity Award of the University of Oregon (1994) and an ACS Arthur C. Cope Scholar Award (1995). When Nelson received the (first) Paul G. Gassman Distinguished Service Award of the ACS Division of Organic Chemistry in 1994, he was being recognized for the years of his time that he had contributed, *inter alia*, to editorial work *(Journal of Organic Chemistry*, *Organic Syntheses, Journal of the American Chemical Society*, *Biochemistry*, *Chemistry International*, and *Pure and Applied Chemistry*) and to committee work on foundations (National Science Foundation, National Research Council, Alfred P. Sloan Foundation, National Institutes of Health, John Simon Guggenheim Memorial Foundation, Searle Scholars Program in the Chicago Community Trust). He was active in the Division of Organic Chemistry of the American Chemical Society and the International Union of Pure and Applied Chemistry. Along with his earned degrees (B.S., 1937, Lehigh University; B.Sc., 1940 and D.Sc., 1983, University of Oxford; Ph.D., Columbia University, 1942), Nelson's honorary degrees included Sc.D. (1963) Lehigh University, Doctor Hon. Causa (1980) Adam Mickiewicz University, Poznan, Poland and D.Sc. (Hon) (1988) University of Illinois, Urbana-Champaign.

Over a period of five decades, Nelson Leonard's research showed him to be a leader rather than a follower, a successful explorer in areas other than organic chemistry but with the advantage of a firm base in synthetic and structural organic chemistry. He was a major force in organic and bioorganic chemistry. Nelson was an awe inspiring personality – an uncommonly handsome man and a genuine gentleman. He was my Ph.D. mentor, my tireless supporter, my role model, my colleague on the Board of Directors of Organic Syntheses, Inc. and my dear friend.

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