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A Biographical Memoir by

GILBERT STORK

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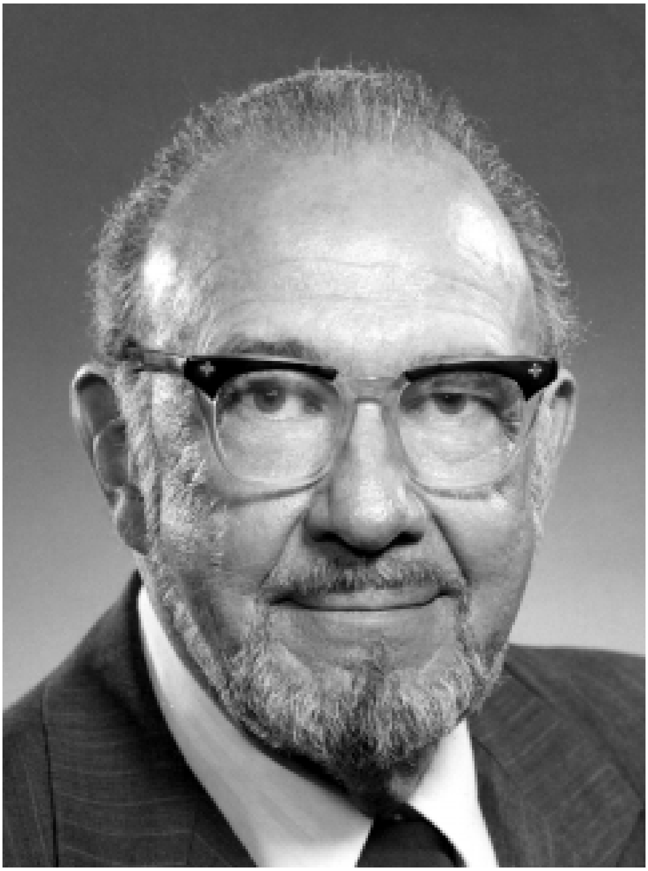

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William S. Johnson

WILLIAM SUMMER JOHNSON

February 24, 1913–August 19, 1995

BY GILBERT STORK

WILLIAM SUMMER JOHNSON, one of the major figures in the development of the art and science of organic synthesis in the second half of the twentieth century, was born in New Rochelle, New York, on February 24, 1913, the second child of Roy Wilder Johnson and Josephine Summer. He received his early education in New Rochelle and finished high school in Massachusetts at the Governor Dummer Academy, which his father had also attended. Bill Johnson showed himself to be a young man of many talents who spent much of his spare time in serious hobbies—from constructing radios, an activity that he mastered when barely a teenager, to developing his considerable musical ability with enough enthusiasm to provide serious competition for his school work. This did not prevent him, however, from getting very interested in chemistry at Dummer and doing well enough to receive a scholarship to be admitted to Amherst.

At Amherst, Johnson's interest in chemistry became specifically focused on organic chemistry. Because this was the Depression, Johnson had to be totally self-supporting. He managed to survive by a combination of scholarships, menial jobs, and playing the saxophone in dance bands in the Catskills, even arranging to pay his way for a round trip to

Europe on a transatlantic liner by playing in one of the ship orchestras. In spite of all these demands on his time, he did well enough as a chemistry major at Amherst to be elected to Phi Beta Kappa in his junior year and to graduate magna cum laude. The chemistry department was obviously quite impressed with Bill Johnson, and he was asked to remain at Amherst an additional year after graduation to teach organic chemistry.

Not surprisingly, Johnson was admitted to the Ph.D. program at Harvard, where he did his research in Professor Louis Fieser's group and began a lifelong fascination with steroids and related polycyclic systems. At Harvard, Johnson who was supporting himself in part by working during the summers as a chemist at Eastman Kodak in Rochester, New York, accomplished the remarkable feat of completing his research work for the Ph.D. in January 1940, after less than two years of residence!

After a few months as a postdoctoral assistant at Harvard with Professor R. P. Linstead, Johnson was appointed instructor in the chemistry department of the University of Wisconsin in Madison, starting in September 1940. Shortly afterwards, on December 27, Johnson married Barbara Allen, whom he had met in Cambridge. This was the beginning of a remarkably successful partnership that lasted some 55 years until Johnson's death. Barbara's extraordinary ability to empathize with people, from small children to the elderly, contributed much to the Johnsons' gift for making every visitor to their home feel welcome and for building long-lasting friendships with most of those who had the good fortune to know them.

After some 20 years as one of the best known members of the chemistry department at Wisconsin, becoming Homer Adkins Professor in 1944, Johnson was known as a great organic chemist, and some of the more perceptive members of chemical academia had also become aware of his administrative skills and of his ability to recognize creative talent in chemists, whether organic chemists or not.

Johnson liked the chemistry department in Madison. When efforts were made to entice him to join Stanford University to build up its chemistry department, he was asked to make a list of requests Stanford would have to meet. I think he hoped subconsciously that Stanford would find them unacceptable. They did not, and Johnson moved to Stanford as professor and executive head of its chemistry department in 1960. As the saying goes, the rest is history. Under Johnson's leadership, helped by the decisive support of Stanford's president, Wallace Sterling, and its provost, Fred Terman, the chemistry department at Stanford succeeded in attracting within just four years individuals like (chronologically) Carl Djerassi, Paul Flory, Henry Taube, Eugene Van Tamelen, and Harden McConnell, so that, even before Johnson relinquished his executive head responsibilities in 1969, the Stanford chemistry department had become one of the top chemistry departments in the world.

Johnson made many contributions to his profession, in addition to the scientific achievements that will be addressed in the following section. Some of these contributions were made in his capacity as chemical consultant with a number of chemical and pharmaceutical companies. Two of the longer lasting of these associations were with the Winthrop Chemical Company, which later became the Sterling-Winthrop Research Institute, and with DuPont. Johnson also contributed much to the American Chemical Society, which he served as chairman of its Wisconsin Section in 1949; as chairman of the Organic Division in 1951; and as a member of the important Committee on Professional Training (1952-56). He also served on editorial or executive boards of numerous Journals: *Journal of Organic Chemistry* (1954-56); *Journal of the American*

Chemical Society (1956-65); *Tetrahedron* (1957-95); *Bioorganic Chemistry* (1971-82); and *Synthesis* (1975-95)**.** He also served on panels of the National Academy of Sciences: the Subcommittee on Synthesis of the Committee for the Survey of Chemistry (in 1964) and the U.S.-Brazil Science Cooperation Program, Office of the Foreign Secretary (1968-72). He, of course, also served both on the Chemistry Advisory Panel of the National Science Foundation (1952-56) and on one of the medicinal chemistry study sections of the National Institutes of Health (1970-74).

SCIENTIFIC CONTRIBUTIONS

In the fall of 1940, when Johnson started his independent career, the concept of controlling the stereochemical course of the reactions envisaged for a particular synthesis belonged to science fiction. The few syntheses of natural products that had been recorded, such as those of camphor, cocaine, glucose, and hydroquinine, were tributes to the brilliant experimental work and courage of the organic chemists who engaged in these difficult journeys, knowing that they would face complex and tedious separations of the various isomers to be expected from their efforts. The extraordinary difficulties they surmounted served to emphasize the improbability of success in attempting to put together the complex structures that were being suggested for a host of natural products. Some brilliant and original chemists of the time handled the problem by concentrating on devising methods to achieve chemical *connectivity*, simply ignoring stereochemistry. They seemed to consider it an unreasonable handicap to the free exercise of their imagination. While they did design important new methods, most of their efforts at total synthesis were doomed to failure. Quite aside from stereochemical control, knowledge had not yet advanced to the point that even regio*selectivity* could be planned.

Johnson, from the very start of his stay at Wisconsin, found himself fascinated by these problems of regio- and stereochemistry. Steroids had become the object of considerable interest by 1940 because of their involvement in many important biological processes, but one of the numerous hurdles to their attempted laboratory syntheses was the presence of methyl groups in the so-called angular positions between certain of their rings. The available methods of methylation had failed to introduce methyl groups selectively at the proper locations: They produced the wrong *regiochemistry*.

Johnson solved the problem by devising an angular methylation sequence, in which an easily introduced temporary controlling group prevented the unwanted regiochemistry. The scheme was successful, but removing the temporary group, after its controlling function had been served, proved difficult. Johnson used his command of mechanistic concepts, some just emerging, to devise a very imaginative sequence of reactions that resolved the difficulty, thus producing the first solution of some generality to an extremely common problem in regioselective carbon-carbon bond formation. Johnson went one step further: He had given a solution to the regiochemical problem, but there remained a stereochemical one. The stereochemistry of the bicyclic system resulting from his regiochemically controlled methylation turned out to be quite cleanly *cis*. How could the angular methylation process be changed to give the *trans* system encountered in natural steroid frameworks? Johnson later concluded, again on the basis of mechanistic considerations, that the desirable *trans* bicyclic system should become the major product if he carried out his angular methylation scheme on a bicyclic system bearing a double bond parallel to the ring junction. This proved to be correct.

I have dwelled on this particular methodology, now mostly of historical interest, because it illustrates that, at the very beginning of his career, Johnson was acutely aware of the important problems that had to be solved to make complex synthesis into a rational endeavor. This early work also illustrates his conviction that attention to reaction mechanism principles is crucial to the design of new synthetic methodology. This work also illustrates his commitment to stay with a problem until a solution is reached.

These qualities served Johnson well in the work for which he is best known, the introduction of carbocation-based chemistry as a powerful tool for the construction of polycyclic systems. At the time Johnson began to contemplate the possibility that cationic polyene cyclization might go beyond the realm of intriguing theoretical speculation, attempts at constructing complex organic structures relied almost entirely on *base-catalyzed* formation of enolate ions derived from carbonyl compounds, followed by their reaction with electrophilic carbon entities. The importance of Johnson's contribution to changing this state of affairs cannot be overemphasized. When he started his work on the cationic cyclization of polyenes, the scattered efforts in this area had convinced everyone but himself that there was no serious possibility that the core of a complex structure like that of a natural steroid, with all the problems, regio- and stereochemical, implied by the existence of six, seven, or more asymmetric centers, could some day be assembled in just one or two steps. And that the process would eventually be able to create a single predictable structure, rather than the several dozen isomers that would result from a random process.

Johnson's extraordinary success in this area was not the result of lucky accidents. It followed a number of many fundamental contributions that benefited the entire field of synthesis. Central to the eventual success was Johnson's recognition that the initiation of the cyclization process was crucially related to the possibility of achieving concertedness in interaction with the multiple olefinic centers in the polyene chain. His brilliant perception was that the high-energy carbocations used to start a polycyclization process by earlier workers were too reactive and unstable to result in stereospecificity or, for that matter, even chemoselectivity, but that less energy-rich and longer-lived á-alkoxy or allylic tertiary carbonium ions might well be much more effective. And, indeed, they were.

The design of effective and useful nucleophilic terminators for the polycyclization process also proved important. There again, Johnson's solutions to the problem were firmly based on mechanistic concepts. They have had an impact well beyond the steroid targets for which they were originally devised: The propargylsilane terminator, which led as he expected to an allene, is a case in point. It was designed not only as an efficient terminator, but the resulting allene, when generated at what would become the steroid 17-position, could be easily transformed to the characteristic dihydroxyacetone side-chain of such adrenal hormones as cortisone.

Johnson's desire to induce not only *stereo*specificity but *enantio*specificity as well led to further important contributions. One of them was the demonstration that the cyclization conditions he eventually devised were sufficiently mild that a single secondary allylic alcohol enantiomer, at the position which would eventually become the 11-oxygen center of a corticosteroid, was able to survive the cyclization process and to induce the correct enantioselectivity *at all the relevant centers produced by the cyclization*.

An even more general contribution to synthesis methodology followed Johnson's study of the á-alkoxy cations he sometimes used to initiate certain polyene cyclizations. This was the demonstration that the alkoxycation derived by cleavage of an acetal made from a homochiral, C2 symmetric, 1,3-glycol can lead to efficient transfer of chirality in its electrophilic attack on an olefin. This resulted in a very useful new method for the formation of enantiocontrolled centers adjacent to a carbon-oxygen bond, such as in the synthesis of optically active á-hydroxyacids.

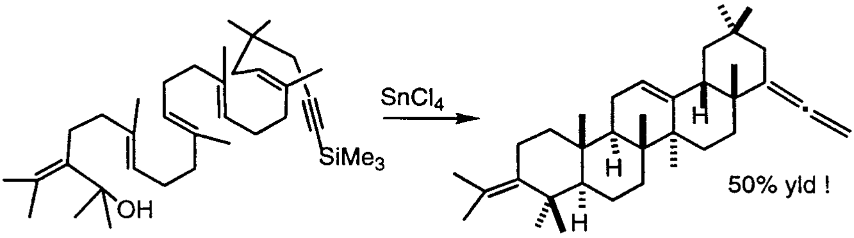
I now refer to three more contributions that originated from problems Johnson encountered in the polyene cyclization work, but which have left their mark much beyond it.

Johnson showed that careful analysis of the E-selectivity resulting from the Julia olefin synthesis of disubstituted olefins strongly suggested that it might also lead to selectivity in the construction of *trisubstituted* olefins, an even more demanding problem. This proved correct, and the resulting process is now called the Julia-Johnson reaction. It was that same insistence on understanding the mechanistic basis of a synthetic operation that led Johnson to invent a process, now known as the Johnson-Claisen orthoester rearrangement, that has led to a great simplification of the venerable reaction known as the Claisen rearrangement. It has achieved great importance because of its experimental simplicity, as well as its ability to control regio- and stereochemistry. It has become a major tool in complex synthesis.

Among the many other contributions of Johnson and his research group, one that has not yet been appreciated as much as it eventually will be, is the realization that a fluorine atom, in spite of its high electronegativity, is very effective in stabilizing an adjacent carbonium ion. So far as I know, this rationalizable but somewhat counter-intuitive fact was first used to major advantage in Johnson’s polyene cyclization work. Johnson took advantage of this remarkable property in his use of the vinyl fluoride terminator (which, in a steroid context, led to the desirable 20-ketosteroid system). Johnson also made highly effective use of a fluorine atom as a controlling substituent to favor a particular cationic center in a desired polycyclization intermediate.

It is not often that a field is created and developed by the work of one individual. There is little doubt, however, that the entire field of controlled synthesis based on cationic polyene cyclization would have lain fallow for a very long time without Johnson's vision, and his absolute dedication to achieving his goal.

Perhaps the most demanding test of someone's contribution to their chosen field is the question, "What can be done or understood now that was not feasible or understood previously?" In the case of William S. Johnson, the answer is, "a lot," as is illustrated, inter alia, in the striking transformation, reported in one of his last papers (1994).



WILLIAM S. JOHNSON—THE MAN

It is, of course, not possible to derive Bill Johnson's human qualities from the important contributions he made to organic chemistry. I have alluded to his love of music. It would lead him to spend the large part of a trip to Paris to search for a rare and highly prized saxophone; to leave a chemical meeting surreptitiously for a visit to a session of a jazz congress where Jerry Mulligan was performing; to engage in friendly and enthusiastic cross-country telephone competition to see who could be the first to identify the artist on a particular jazz recording; or to join a few other talented musicians like Harry Wasserman and Richard Turner to produce memorable spur-of-the-moment performances. Johnson took great pride in the extremely high quality of the electronic equipment, especially the loudspeakers, that he had carefully positioned in the living room of the beautiful home he shared with Barbara in Portola Valley.

Johnson was an outstanding teacher. Not only because of his command of the material but also because of the passionate enthusiasm he had for his subject and the deep interest he had in his students. This was especially evident in his interaction with his graduate students and postdoctoral associates who became in effect part of his family. Many, like David Gutsche, Ralph Hirschmann, Hans Wynberg, Robert Ireland, Richard Franck, James Marshall, John Keana, Kathlyn Parker, Martin Semmelhack, Paul Bartlett, Bruce Ganem, and Glenn Prestwich, became themselves leaders in their field in academia, while many others, such as Barry Bloom, Raphael Pappo, Jacob Szmuszkovicz, John Pike, and J. W. Scott, made their marks in industry.

Bill Johnson's love of chemistry, and his empathy for kindred spirits, had happy consequences, as on the occasion of the visit of Professor John D. Roberts of Caltech to Madison, as Folkers Lecturer. The interaction resulted not only in the lifelong friendship of Bill and Barbara with Jack and Edith Roberts, but also in the joint authorship of a communication on the acid-catalyzed methylation of alcohols with diazomethane (M. C. Caserio, J. D. Roberts, M. Neeman, and W. S. Johnson, "Methylation of Alcohols with Diazomethane," *J. Am. Chem. Soc.* 80:2584-85, 1958).

My wife, Winifred, and I enjoyed deep friendship with the Johnsons. The word friendship in fact seems inadequate. It certainly survived some unusual stress. One such instance

I remember well was on the occasion of the celebration in New York of the centennial of the American Chemical Society. Johnson, the last of the distinguished speakers, was just starting to address the large crowd in the darkened hotel ballroom, when word came to the organizers that the hotel needed to have the room vacated within five minutes to prepare for a scheduled wedding. The frantic organizers, who knew of my friendship with Johnson, begged for my help, and I climbed on the darkened stage to tell the startled Johnson that his just-begun lecture was over. Our friendship survived, and by the time Bill Johnson died, it had lasted over half a century.

AWARDS AND RECOGNITION

Many prestigious honors came to Johnson in acknowledgment of his scientific stature. Among the most notable was his election to the National Academy of Sciences as early as 1952. He was also a member of the American Academy of Arts and Sciences; received both the Roger Adams and the Arthur C. Cope awards; the Award for Creative Research in Organic Chemistry; the Tetrahedron Prize for Creativity in Organic Chemistry; and the Nichols Medal. A particularly significant recognition came when he was selected by an international jury in France to be the first recipient, in 1970, of the Roussel Prize for Steroid Chemistry. Another award that he must have particularly prized was this country's highest award in science, the National Medal of Science, which he received in 1987. This list is not exhaustive, but it should include the annual, highly successful Johnson Symposium, which Johnson's colleagues at Stanford started in his honor in 1986. It was a gesture that touched him deeply.

The title Johnson chose for his autobiographical memoir was "A Fifty Year Love Affair with Chemistry." The love was obviously reciprocated.

SOME OF THE introductory biographical material has been gathered from W. S. Johnson’s fascinating autobiographical account of his life in chemistry: *A Fifty Year Love Affair with Chemistry*. Washington, D.C.: American Chemical Society, 1998.

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