Marshall D. Gates Jr.

1915-2003

BIOGRAPHICAL *Memoirs*

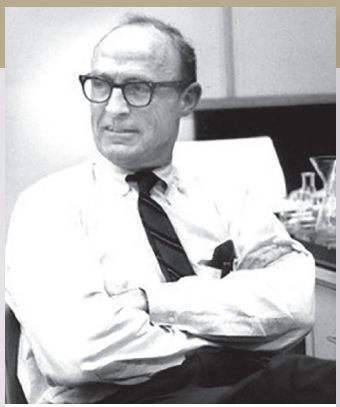
A Biographical Memoir
by Richard Eisenberg
and Alison Frontier

NATIONAL ACADEMY OF SCIENCES

MARSHALL DEMOTTE **GATES JR.**

September 25, 1915–October 3, 2003

Elected to the NAS, 1958



Photograph by Richard Eisenberg

By Richard Eisenberg and Alison Frontier

Marshall D. Gates was a seminal and thoroughly engaging figure in twentieth-century organic chemistry. Gates was the first chemist to synthesize morphine, which was known to be both a great pain reliever and an addictive drug. The synthesis was viewed at that time as a landmark achievement in natural products synthesis. Gates also served as editor and then editor-in-chief of the *Journal of the American Chemical Society (JACS)* in the 1950s and 1960s, during its period of impressive growth as research efforts in the field blossomed. This long-overdue memoir is written by two chemists at the University of Rochester, one a personal friend for many years, and the other a younger faculty member specializing in organic synthesis who knew of Marshall's work on morphine but met him only once. This tribute is also helped in an unusual way by Gates himself, who wrote an autobiography for his family and our university. Gates undertook this task after reading one composed by his great-grandfather, whose life during the nineteenth century Gates found riveting and illuminating.

Gates was born on September 25, 1915, in Boyne City, Michigan. He had his first introduction to organic chemistry when he was an undergraduate at Rice Institute (now Rice university). He found the subject's foundations and its three-dimensional structural aspects, together with its deductive reasoning for producing compounds having such structures, stimulating and appealing. During his time at Rice, he started to read the research papers of Louis Fieser at Harvard University and resolved to go to Cambridge, Massachusetts, to join his group and pursue a Ph.D. there. That part of Gates' life began in the fall of 1938 (the year Marshall met his future wife, Marty, as well), and he described the time of his graduate studies as among the happiest of his life.

Initially, work with and under Fieser's mentorship included studies on carcinogenic hydrocarbons and quinones, including the quinonoid Vitamin K. (There was also work on exotic explosives under Fieser's government contract that Gates and fellow graduate student Bill Doering investigated.)

Following graduate work in the Fieser laboratory, Gates was set to assume an instructorship at Harvard when an opening at Bryn Mawr College occurred. Arthur C. Cope, then the organic chemistry faculty member there, was leaving for a position at Columbia University, and Fieser recommended Gates for the position (Fieser had preceded Cope at Bryn Mawr, so there were only positives to teaching there for a career that would involve both research and teaching). Gates found the appointment, together with marriage to his life-long partner, to be truly idyllic.

Figure 1: Gates in the laboratory in the 1950s during completion of morphine synthesis. (Photograph courtesy of Richard Eisenberg.)

The outbreak of World War II changed many things for many people, and for Gates, this led to joining a division of the National Defense Research Committee (NDRC) to examine and assess projects related to offensive and defensive aspects of chemical warfare (which were fortunately not used in World War II). In light of what had happened in World War I, it was thought necessary to carry out research in this area of chemical science. Senior associates of the NDRC included true notables of American chemistry, such as Roger Adams, Arthur Cope, Carl Marvel, and Albert Noyes, the last of whom played a key role in bringing Gates to the University of Rochester and ultimately to the editorship of the *JACS*. It was also during this period that Gates, cut off from the laboratory work that he so enjoyed, formulated the idea that ultimately led to his most important research achievement—the synthesis of the alkaloid morphine. The structural formula of this historically and chemically important compound had been put forward by Sir Robert Robinson, but proof through synthesis remained a notable challenge.

The post-war years witnessed a growing interest and activity in organic chemistry, which in turn led Noyes, a physical chemist who was to become the *JACS* editor, to contact Gates about moving to Rochester and becoming an assistant editor to handle all of the "organic" submissions. The negotiation included a faculty position at the University of Rochester, as well as his own laboratory and the opportunity to work with graduate students and postdocs. The situation proved ideal in that Gates could pursue his interest in synthesizing morphine while at the same time serving as the editor for organic chemistry-related research in *JACS*.

In 1870, a sizeable reward had been offered by the Prussian Academy of Science to anyone who could synthesize morphine, but the task proved so difficult that it was not accomplished until eighty-two years later, with the disclosure of the landmark Gates synthesis.[2] By that time, there was no such monetary prize, with only the scientific reward remaining. The work followed a report of a simplified version of the molecule without oxygen atoms, described in 1946 by W. F. Newhall at Brandeis University. Building upon this foundation, Gates and Swiss graduate student Rosemary Kunzli embarked upon the synthesis of the exact structure of morphine proposed by Robinson. Then, according to Gates, the final member of the team was recruited: "When it came time for Rosemarie Kunzli to return to Switzerland, she arranged for a friend of hers [who Gates did not know was engaged to Kunzli as well], Gilg Tschudi, a young doctorate from the Swiss Federal Technical Institute in Zurich, to come over as a Post-doctorate Fellow to work with me." In August 1950, Tschudi and Gates obtained conclusive evidence (through degradation studies) that they had assembled an advanced intermediate with both the correct carbon skeleton and all oxygen and nitrogen atoms in place. Gates, working alone, successfully converted this intermediate to morphine in January 1952.

About his achievement, Gates later wrote,

> *A word or two about the morphine synthesis: We did not set out to find a synthesis which would supplant or compete with the natural source, the opium poppy (Papaver somniferum) and indeed this would be well-nigh impossible, natural morphine is very easily and cheaply obtained (our synthesis is some 27 steps some of which proceed in only modest yield). The purpose was to prove the structure of the alkaloid which at the time we began was not certain in all respects. Nowadays the structures of crystalline substances are demonstrated by X-ray crystallography but this method was not then successfully applicable to substances as compli-cated as morphine owing to the laborious calculations required which became routine only with the advent of high-speed computers. An X-ray crystallographic structural determination of morphine was carried out only some years after our synthesis was completed. The traditional proof of structure then was an unambiguous synthesis which was what we had undertaken.*

As the chemistry of the alkaloids was elucidated in subsequent years, Gates learned that synthetic opiates bearing an N-allyl substitution pattern were narcotic antagonists, rather than agonists. Knowing that the chemical properties of allyl and cyclopropyl groups were similar, he was inspired to prepare and study N-cyclopropyl morphinan derivatives. In the early 1960s, this line of inquiry struck gold when the Gates group found that their new molecules possessed very interesting pharmacological properties. Their substances exhibited substantial analgesic activity and much reduced addiction liability, but also caused hallucinations. Gates' work on N-cyclopropylmethyl derivatives constituted early steps toward the discovery of naltrexone, an important drug for treating addiction to opiates and other substances of abuse.

During the early phases of his editorial work for *JACS,* Gates handled the organic-related submissions to the journal, which included correspondence with numerous researchers and leaders in the field. One notable exchange was with his good friend Robert Burns Woodward regarding the unprecedented "sandwich" structure for ferrocene that Woodward proposed. Gates wrote: "We have dispatched your communication to the printers but I cannot help feeling that you have been at the hashish again."

In 1962, Gates became the editor-in-chief of *JACS* following the retirement of Albert Noyes. Gates carried out his duties with a very limited number of associate editors (and a small office staff at the Rochester Chemistry Department). During his time in this role, he served as a mediator between notable scientists such as H. C. Brown, D. Cram, and others on the strongly contested matter of carbonium ion intermediates.

At the same time and afterwards as well, Gates taught the large introductory organic chemistry course and conducted additional research on the synthesis and characterization of morphine derivatives and related compounds. Gates always enjoyed laboratory work himself, so his research group remained small, focused, and productive, a model different from today's leading investigators with multi-focused mega-groups. Among alumni from the Gates research group are Gilg Tschudi, Rosemary Kunzli, Bill Webb, John Zabriskie, Bill Pirkle, Dick Partch, Don Arnold, Steve Weinreb, Tom Montzka, Yvon Perron, Anthony Roe, and Max Hughes.

In recognition of his groundbreaking work in the synthesis of morphine and related derivatives, Gates was elected to the National Academy of Sciences in 1958. He was also elected to Fellowship in the American Academy of Arts and Sciences. In 1968, Gates was appointed to the President's Committee on the National Medal of Science, during which he remembers recommending Linus Pauling for the award, but it was turned down by

both Presidents Johnson and Nixon for Pauling's opposition to the Vietnam War! Importantly, for his teaching of the large organic chemistry course for non-majors, most of whom were pre-medical students, he was recognized with the University of Rochester's Curtis Award for Excellence in Undergraduate Teaching. Gates proved himself in many venues as a very special colleague, chemist, teacher, and friend. He retired in 1981 but continued to conduct research as an emeritus professor.

Gates was an avid sailor and skier, and he also was a master glassblower, creating many of the instruments he used in his laboratories. He also enjoyed building model wooden sailboats and maintained a weekly poker game for more than 35 years.

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