Harry H. Wasserman

1920–2013

BIOGRAPHICAL *Memoirs*

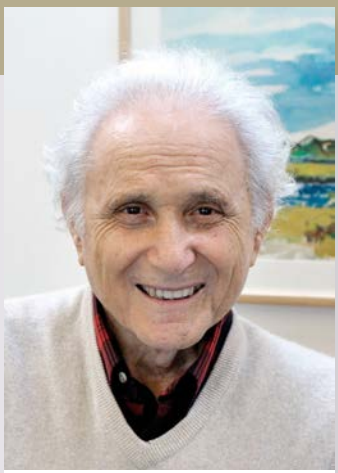
A Biographical Memoir by
Jerome A. Berson
and Samuel J. Danishefsky

NATIONAL ACADEMY OF SCIENCES

HARRY HERSCHAL **WASSERMAN**

December 1, 1920–December 29, 2013

Elected to the NAS, 1987



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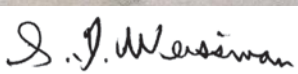


By Jerome A. Berson and Samuel J. Danishefsky

Harry Wasserman—a warm, charming, multi-talented man and a keenly creative chemist—served on the faculty of Yale University for more than 50 years. Harry grew up in and around Boston, MA, in a family that often struggled to pay the rent. On weekends, he and his brothers would earn a few dollars sifting sand on nearby Revere Beach for lost coins. He earned high marks at Cambridge & Latin high school and was awarded a Cambridge scholarship to the Massachusetts Institute of Technology, which he entered in 1937 at age 16. He earned a B.S. in chemistry from MIT in 1941. While in college, Harry considered a career as an artist, and he studied with Boston painter and sculptor John Wilson, but science, particularly chemistry, drew him away from a full-time commitment to art. He continued to follow both muses throughout his life. After MIT, Harry began graduate studies at Harvard University under the mentorship of the organic chemist Robert Burns Woodward, a future Nobel laureate, Harry interrupted his graduate studies in 1943 to serve in the 503rd Army Air Force in Africa and the Middle East. He rose to the rank of captain and trained soldiers across the region to detect chemical gas attacks and protect themselves accordingly. Returning to Woodward's lab after the war, Harry met Elga Steinherz, a fellow member of the research group. They were married in 1947. Upon completion of his Ph.D. research in 1948, Harry joined the Yale University faculty (he received the degree in 1949). Over the subsequent years, he and his research group at Yale developed innovative methods for synthesizing antibiotics and other natural products. His many significant discoveries and accomplishments earned him great recognition and respect from his colleagues, and he received numerous awards and other honors throughout his career.

At Yale

Research and teaching in chemistry at Yale in the immediate postwar period were particularly strong in physical chemistry, as exemplified by the work on the physical

New Haven, Connecticut.
By Harry H. Wasserman.

properties of ionic solutions led by John Gamble Kirkwood and Lars Onsager. The school's organic chemistry, however, had lost the leadership of Treat Baldwin Johnson, who died in 1947, and the discipline at Yale needed rebuilding. New strength was added to the organic faculty with the acquisition of William von Eggers Doering from Columbia University in 1952 and, a decade later, Kenneth Berle Wiberg, a former Doering student, then at the University of Washington. Although Harry's first position at Yale was as an instructor of chemistry, by 1962 he was a full professor, his leadership qualities were evident (he had served for a time as chairman of the chemistry department), and he was instrumental in recruiting Wiberg, who became a close friend. Subsequently, the department went through a period of sturdy growth, in which both of them contributed decisive insights to the choices of new colleagues.

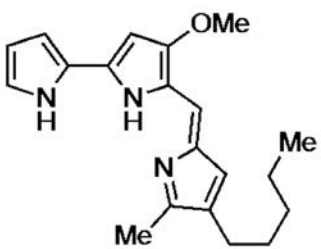
As a pioneering editor

In the period from just before World War II to more than a decade after, publication of research articles on chemistry often was handicapped by long delays and, in some cases, the imposition of an editor's personal judgment in the evaluation process. Pergamon Press and its leader Ian (later Robert) Maxwell agreed to adopt a new approach, in which the objective of the journal was to encourage and facilitate the rapid publication of refereed, high-quality, original research. As a result, Pergamon announced in 1959 that it would be bringing out just such a journal in organic chemistry under the name *Tetrahedron Letters*. Its honorary founding editors were Sir Robert Robinson and Harry's mentor Woodward, and they chose Harry to be American editor. He served in that post for 38 years (1960–1998), during which time, it has been estimated, some 10,000 articles passed through his office on the third floor of Yale's Sterling Chemistry Laboratory, were carefully examined and refereed, and, if found deserving, sent off to press. In cases of disagreement between authors and referees, Harry often found ways to resolve the conflict constructively by suggesting modifications that would satisfy both sides. Thus he was a peacemaker who used such situations as teachable moments. He certainly was among the first to provide graphic illustrations in the abstracts at the top of each paper, thereby giving the reader an instant clue about the relevance of the work to his or her own interests.

As a research scientist

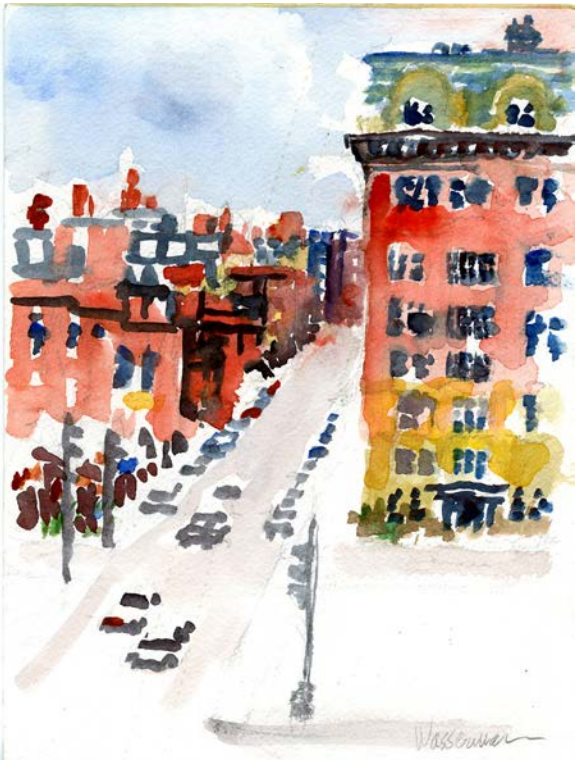
I. Prodigiosin

Though Harry was most widely known for his works in chemical synthesis, he had a real passion for structure determination. Indeed, he was ever on the lookout for natural products of promising biological activity and seemingly challenging structural motifs. While space does not allow us to develop this theme broadly, clearly his favorite natural product, from the structure standpoint, was prodigiosin, a red pigment isolated from the bacterium *Serratia marcescens*. It may be of interest to put Harry's prodigiosin program in the context of the state of organic chemistry when his career as an instructor began at Yale in the early 1950s. By any standard, the postwar era witnessed an exhilarating expansion in the powers of organic chemistry, but as Harry was entering the structure determination field, the need for degradative strategies—wherein larger structures are inferred from smaller



Prodigiosin

fragments—was still prevalent. Already in place were the powerful tools of ultraviolet (UV) and infrared spectroscopy. These spectral measurements allowed one to clarify the presence or absence of key functional groups without conducting a chemical reaction. On the horizon were the emerging and even more powerful resources of nuclear magnetic resonance (NMR) and mass spectrometry—methods that would provide the capacity to deal with problems of actual bond connectivities in structure determination. Yet even with the advent of these transforming technologies, at that early stage the structure determination of unknowns still required a very high level of expertise in classical chemistry. One had to be able to recognize diverse outcomes arising from treatment of the unknown target structure with available reagents, usually oxidizing agents (such as ozone, $KMnO_4$, and OsO_4). Similarly challenging was the need to deduce how organic structures might respond to challenges from confrontation with simple hydrolytic agents (acids or bases), often under highly forcing conditions. Helping to enable these sorts of deductions was what was euphemistically called "electron-pushing"—an attempt to reduce the emerging teachings of mechanistic organic chemistry to formalisms, expressed as "curved arrows," that purported to explain how chemical transformations took place. Harry practiced this science/art form with great skill (and relish). In retrospect, the capacity to provide an accurate structural determination of rather complex molecules, with the modest spectral resources then available, must be seen as remarkable. It is in this setting that we review some of Harry's early work in the prodigiosin series.



Boston, Massachusetts.
By Harry H. Wasserman.

From early in his career, Harry was interested in prodigiosin, both in determining its structure and in its chemical synthesis. Ultimately, combining his analytical talents with the pioneering use of NMR and UV spectroscopy technologies, Harry was able to determine the structure of prodigiosin—in 1960 (Wasserman et al. 1960). Insights from this study and further structural studies (Wasserman et al. 1966a) led Harry to synthesize a series of compounds from the prodigiosin family over the next decades, including undecylprodigiosin (Wasserman, Rodgers, and Keith 1966b), metacycloprodigiosin (Wasserman, Keith, and Nadelson 1969), and cycloprodigiosin (Wasserman and Fukuyama 1984). As the spectroscopic technologies continued to improve, Harry incorporated new methodologies into his structural studies. With the introduction of more advanced ^{13}C NMR techniques, Harry utilized the new technology to assign the carbons of the prodigiosins (Cushley et al. 1975).

II. Small ring synthesis

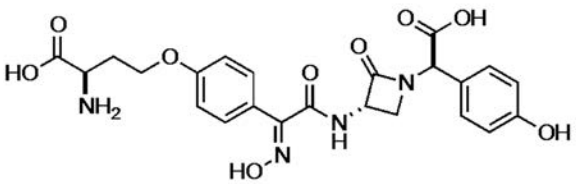
A major focus of Harry's career was small strained rings—in particular, oxidized cyclobutanes, cyclopropanone surrogates, and azetidines, the latter of great value to him as surrogates for two azetidinones. But as we argue below, ß-lactams were perhaps Harry's most compelling long-term research interest.

In a major triumph, Harry discovered a one-step mechanistically predicted cycloaddition of the then newly emerging alkoxyacetylenes with ketenes. Following hydrolysis of the resulting enol ether linkage, the otherwise inaccessible cyclobutane 1,3-dione series became available in two simple steps (Wasserman and Dehmlow 1962a,b). While seemingly obvious now, at that time it took a great deal of insight to achieve these kinds of targets in such an elegant fashion.

Another approach to the cyclobutane series started with cyclopropanone surrogates. Harry found that hemiketals of cyclopropanone could serve as electrophiles for nucleophilic addition of Grignard reagents (Wasserman and Clagett 1966). These cyclopropanol intermediates could then undergo expansion to provide another route to various cyclobutanones (Wasserman, Cochoy, and Baird 1969).

Another application of the cyclopropanone surrogates was in their transformation to azeditines. This method, which could also be used to produce these scaffolds with the addition of azide to a cyclopropanol intermediate (Wasserman and Baird 1971), in turn became one of Harry's favorite routes to ß-lactams. He saw ß-lactams as the ideal targets for bringing organic chemistry's rising powers to bear on the synthesis of pharmaceuticals, particularly critically needed antibiotics.

It was in this context that Harry also pursued, with great success over many years, the more complicated nocardicin series—a family of monocyclic ß-lactam compounds shown to have broad-spectrum activity against Gram-negative bacteria. By applying an efficient cyclopropanone methodology that he devised, Harry was able to produce 3-aminonocardicinic acid in far fewer steps and better yields than any other approach previously reported (Wasserman and Hlasta 1978). Despite the elegance of this route, Harry continued to pursue other syntheses of the nocardicin series using other ß-lactam methodologies developed in his laboratory (see below).



Nocardicin A

III. 1,2,3-tricarbonyl chemistry

A later interest of Harry's was in 1,2,3-tricarbonyl systems, a field that he virtually invented.[1] The synthesis of 1,2,3-tricarbonyls and their remarkable chemistry were a logical extension of his enjoyment of all sorts of strategies for the formation of carbon bonds by acylations, particularly acylation/oxidation combinations. His initial contribution to the field was his discovery in the mid-1980s that tricarbonyl esters could be prepared by the reaction of dimethylformamide dimethylacetal with ß-keto esters, followed by oxidative cleavage of the carbon-nitrogen double bond with singlet oxygen (Wasserman and Han 1984a). This discovery began his more than 20-year-long program focused on the synthesis and reactivity of this scaffold, as well as its application in numerous chemical syntheses. Later additions to the methodology focused on forming vicinyl tricarbonyl moieties from simple carboxylic acids. One particularly useful contribution combined carboxylic acid starting materials with ylides leading to an equilibrium mixture of the target tricarbonyl and its hydrate, which could then undergo a variety of reactions with nucleophiles to provide a number of valuable methodologies.

This unique scaffold of three adjacent carbonyl moieties provided opportunities for the development of many reactions through the addition of nucleophiles to the highly electrophilic center functional group. In particular, Harry was interested in intramolecular cycloaddition reactions and their application to natural product syntheses. Happily, he was able to apply his notable accomplishments in the invention and development of 1,2,3-tricarbonyl systems to a host of natural product syntheses. Harry reached quite complicated heterocyclic motifs, including particularly complex alkaloids. In an early

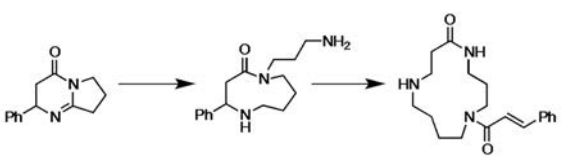
example of this program and in keeping with his love of the ß-lactam scaffold, he applied new tricarbonyl cycloaddition methodology to the synthesis of fused ß-lactam antibiotics used in the partial synthesis of the antibiotic (±)-PS-5 (Wasserman and Han 1984b). A further extension of this methodology led to the development of twofold nucleophilic additions of amino donors, such as phenethylamine and tryptamine derivatives, leading to isoquinoline and indole structures, respectively. (Wasserman and Kuo 1992, 1989; Wasserman et al. 1989a).

In a form of scientific poetic justice, Harry was able to apply his achievements in 1,2,3,-tricarbonyl chemistry in the synthesis of prodigiosin (Wasserman and Lombardo 1989). This synthesis grew out of his program focused on the vinyl vicinyl tricarbonyl scaffold, a dielectrophile that offered a number of opportunities for novel reaction development (Wasserman et al. 1989b). Particularly impressive was his methodology of pyrrole formation by nucleophilic attack with amines through pyrrolidone intermediates (Wasserman et al. 1989c). Harry produced an elegant synthesis of prodigiosin by exploiting the reaction of a vinyl vicinyl tricarbonyl intermediate with a benzylamine to rapidly form the dipyrrole core, leading to natural product in short order.

Harry continued to build on his 1,2,3-tricarbonyl projects well into the 1990s with applications in other fields, such as chemical biology. For example, the highly electrophilic nature of the scaffold was found to be amenable to rapid binding of bis vicinyl tricarbonyls to DNA, leading to interstrand DNA crosslinks (Wasserman and Baldino 1995).

IV. Alkaloid synthesis/zipper motifs

Another of Harry's scientific romances centered around novel settings for trans-acylation of various acyl acceptors. He was an early advocate of designing molecular setups, reminiscent of zippers, wherein medium-sized cyclic amides could be rearranged to build macrocycles. Using these methods, his team built a collection of alkaloid-type structures in a remarkably concise fashion. In 1980, Harry put this idea to work in the synthesis of a spermidine alkaloid—celacinnine—a 13-membered macrolactam. The macrocycle was assembled through a series of two alkylation/transamidation sequences to expand the ring in successive fashion from a 6-membered ring to a 9-membered ring and then again to the

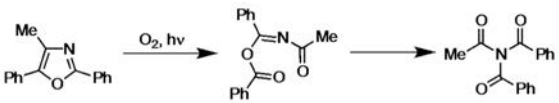


Double Ring expansion leading to celacinnine

required 13-membered macrocycle (Wasserman, Robinson, and Matsuyama 1980). Using a similar approach, he elegantly synthesized in short order other polyamine alkaloids, including (±)-dihydroperiphylline (in just six steps) (Wasserman and Matsuyama 1981), lunarine, and chaenorhine (Wasserman, Robinson, and Carter 1983), as well as many kinds of related alkaloids.[2]

V. Oxidations via singlet oxygen

Certainly, one of Harry's enduring interests was in transformations induced by the action of singlet oxygen on various heterocycles. Particularly remarkable examples of this type of chemistry were realized in the oxazole area. Early in his career, Harry discovered that oxazoles undergo photo-oxidation under mild conditions to produce triamides through isoimide intermediates (Wasserman and Floyd 1966). These triamides were essentially activated carboxylic acids, which opened the door to their use as acylating reagents in a variety of applications. Through singlet oxygen chemistry, Harry was able to exploit diaryloxazoles as staging points for assembling a whole host of targets, including complex macrolides such as recifeidolide (Wasserman, Gambale, and Pulwer 1981) and antimycin A3 (Wasserman and Gambale 1985). He was not only interested in the syntheses utilizing this remarkable chemistry but he also devoted a great deal of time to probing their mechanisms (Wasserman, Pickett, and Vinnick 1981). Mechanistic studies of these complex rearrangements fascinate organic chemists even today.



Oxazole photo-oxidation to form triamide

As seen above, Harry explored widely yet also deeply. His masterful grasp of mechanisms was coupled to an almost artistic flare for intuiting and anticipating novel chemical outcomes. His influence will long endure.

Harry's scientific honors and distinctions included: fellow of the American Academy of Arts and Sciences; member of the National Academy of Sciences; member of the board of directors of the Camille and Henry Dreyfus Foundation; Guggenheim Fellowship, 1959; Chemical Manufacturers Association Catalyst Award, 1985; American Chemical Society Aldrich Award in Synthetic Organic Chemistry, 1987; American Chemical Society Cope Scholar Award, 1990; and National Institutes of Health Merit Award, 1994.

As a teacher, artist, and musician

Harry taught organic chemistry in the classroom for more than four decades, gaining admiration for making an often-dreaded course clear and enjoyable. Among his teaching awards and accolades were Yale's Devane Medal for excellence in teaching and a Yale College Prize for Distinguished Undergraduate Teaching. In honor of his celebrated career, Yale University established the Wasserman Prize for Excellence in the Teaching of Chemistry.

Harry's students and colleagues remember him as a genial and witty friend and mentor, fascinated by the beauty of structures, natural and technological alike. He

Cape Cod, Massachusetts. By Harry H. Wasserman.

was ever upbeat, down-to-earth, and game for adventure, whether beachcombing for driftwood treasure with the kids and grandkids on Cape Cod or exploring museums and

marketplaces with Elga. He savored good stories, a firm handshake, Benny Goodman, Humphrey Bogart, and the Marx Brothers.

Harry traveled widely for his science, and when on the road he always took his brushes and sketchbooks. He would often delight family and friends with letters or postcards illustrated with watercolors of people, ports, and landscapes. His paintings of campus architecture graced the cover of the Yale summer course catalog for 15 years. Jazz was another of Harry's lifelong passions. A self-taught clarinetist, he played regularly with a number of jazz combos, including a quartet of Yale chemists performing as "the Gloom Exterminators."

Harry died in 2013 and his beloved wife Elga passed away the following year. They are survived by their children Daniel, Diana, and Steven; seven grandchildren; a great-granddaughter; and Harry's brother Herbert.

Granada. By Harry H. Wasserman.

ACKNOWLEDGEMENTS

We thank the Wasserman sons for their eloquent obituary (www.legacy.com/obituaries/nytimes/obituary.aspx?page=lifestory&pid=168878423) and for permission to quote from it. Supplementary information was kindly provided by colleagues at Yale and elsewhere.

ENDNOTES

1. For a review of Wasserman's contributions to tricarbonyl chemistry, see Wasserman and Parr, 2004.
2. For a review of Harry's zipper approach to macrolactams, see Wasserman and Wu, 1982.

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