PROFILE AND SCIENTIFIC CONTRIBUTIONS OF PROFESSOR R. B. WOODWARD

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This year, hundreds of organic chemists from all parts of the world have been paying tribute to their former mentor, R. B. Woodward, on the occasion of his 60th birthday. Few individuals in the history of science have had such widespread influence on the development of a major school of research, and on the careers of so many investigators. In the 40 years that he has been at Harvard, over 350 co-workers have been associated with R. B. Woodward as graduate students or postdoctoral associates. Add to this list individuals who have worked with him at the Woodward Research Institute in Basel and the number reaches 400. These chemists, two-thirds of whom occupy faculty positions throughout the world, include some of the most distinguished investigators in the field of organic chemistry.

Woodward rose to prominence in the field of organic chemistry primarily because of his accomplishments in the total synthesis of very complex natural products. There are many reasons for his success in this demanding field. Among them

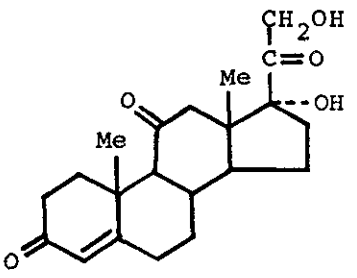
are his mastery of all available physical and theoretical methods, an exhaustive knowledge of the organic chemical literature, and a tireless dedication to problem solving. In particular, Woodward was the first to take advantage of modern electronic theory of reaction mechanisms to guide him through the obstacle-strewn pathways of organic reactions. At the same time he was one of the first to recognize the power of methods such as ultraviolet, infrared, and nuclear magnetic resonance spectroscopy for the determination of structure. These approaches, combined with his rigorous intellectual analysis of the entire synthetic route, including close attention to stereochemical factors, led to an astonishing series of synthetic accomplishments. The following are selected examples.

Syntheses

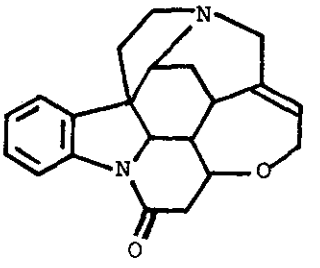
Quinine 1944	Reserpine 1956
Patulin 1950	Chlorophyll 1960
Cholesterol 1951	Tetracyclines 1962
Cortisone 1951	Colchicine 1963
Lanosterol 1954	Cephalosporin C 1965
Strychnine 1954	Vitamin B_{12} 1972
Lysergic acid 1954	Prostaglandin F_{2a} 1973

His first major synthesis was that of quinine with W. E. Doering in 1944. This was followed by sempervirine (1949), patulin (1950) and then in 1951, the total synthesis of the steroid, cortisone. The steroid synthesis was particularly noteworthy in that it produced the difficult-to-achieve functionality at the 11-position and solved a very challenging stereo-

chemical problem, since the six asymmetric centers in cortisone permit 64 possible optically active isomers.

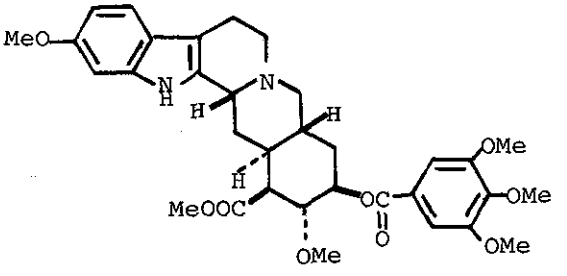


cortisone



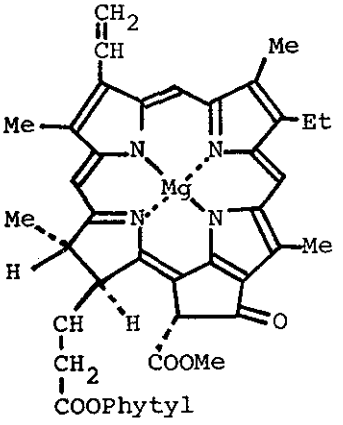
strychnine

In 1954, a total synthesis of strychnine was completed. This was followed by lysergic acid (1954) with a group at Eli Lilly Company, and then, in 1956, reserpine. The reserpine synthesis, accomplished in one year and providing the alkaloid in high yield with complete stereoselectivity at all of its six asymmetric centers, is a masterpiece among many elegant natural product syntheses.



reserpine

Woodward's next synthetic objective was the green pigment, chlorophyll. This synthesis (1960), in contrast to earlier methods of constructing porphyrins which gave low yields of complicated mixtures, involved the preparation of two units, each containing two different pyrroles, which were joined in an unambiguous manner to form the large ring. One of the final steps in this work involved a photochemical oxidation carried out by Woodward himself in one of his rare exercises at the laboratory bench.



chlorophyll

In reviewing Woodward's published work at the time he received the Nobel Prize (1965), Professor Lord Todd noted:[1]

> This is surely a record without parallel in the annals of synthesis, for all these substances, like the steroids, are compounds of very great complexity; indeed, in the case of strychnine and lysergic acid there were many who were doubtful whether synthesis could ever be achieved. *In these papers one* sees organic chemical methods of synthesis brought to their highest peak of perfection.

Among the next synthetic achievements which followed the successful chlorophyll synthesis were the tetracyclines (1962), colchicine (1963) and cephalosporin C (1965). Then followed the synthesis of vitamin B-12. This task, accomplished in collaboration with Professor A. Eschenmoser of the ETH (Zurich), was 11 years in completion and involved 100 co-workers.

Woodward has always looked on organic synthesis as a fruitful medium for discovery of new methods and principles. Informally[2] he has stated his view of the role of this discipline.

> Now chemical synthesis always has some element of planning in it. But the planning should never be too rigid. Because, in fact, the specific objective which the synthetic chemist uses as the excuse for his activity is often not of special importance in the general sense; rather, the important things are those that he finds out in the course of attempting to reach that objective.
>
> And so it is this role of synthetic chemistry in providing a kind of matrix within which discovery can be made which I think is perhaps its most important role for the chemist....

One can find many examples in his work of new discovery: the development of synthetic methods (peptide synthesis through isoxazolium salts, 1961); the pioneering of new techniques (liquid chromatography in the vitamin B-12 work); the elucidation of reaction mechanisms (the Diels-Alder reaction; the dienone-phenol rearrangement). Perhaps the most exciting discovery derived from Woodward's research is the principle of orbital symmetry governing the stereochemistry of concerted organic reactions. Development of the Woodward-Hoffmann rules which were first proposed (1965)

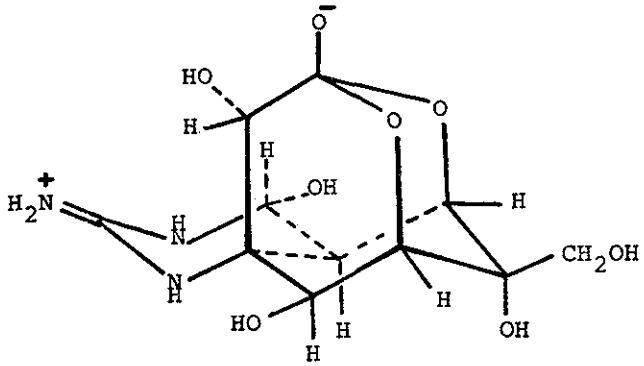
during an analysis of puzzling stereochemical results in the vitamin B-12 synthetic work, represents one of the most important basic theoretical advances in the entire history of organic chemistry.

At the same time that Woodward was engaged in synthesizing molecules of great complexity he also undertook a series of challenging structural investigations. The following is a list of selected natural products, the structures of which he elucidated during the period 1945-1964.

Structure Determinations

Penicillin 1945	Magnamycin 1956
Strychnine 1948	Gliotoxin 1958
Patulin 1959	Oleandomycin 1960
Terramycin 1952	Streptonigrin 1963
Aureomycin 1952	Tetrodotoxin 1964
Cevine 1954	

Starting with penicillin, which he studied during the cooperative research project of World War II, he proceeded to tackle the toughest of the structural problems among the antibiotics, alkaloids, macrolides and fish poisons.



tetrodotoxin

In his strychnine determination he demonstrated the power of U.V. spectroscopy, while in the terramycin investigation he made extensive use of acidity measurements as well as U.V. and I.R. spectroscopy. All through Woodward's structure work one finds examples of his brilliant reasoning which, combined with the refined use of all available physical methods, led to the solution of such complex structures as magnamycin and tetrodotoxin. Today, Woodward would agree that X-ray crystallographic techniques, when applicable, represent the most effective way of gaining structural information. He has, in recent work, made extensive use of X-ray methods in determining the structures of intermediates in the vitamin B-12 synthesis.

Woodward's interests in organic chemistry have been broad, and have ranged from the physical to the biological borders of the field. At the very outset of his career (1941) he published the famous "Woodward's Rules" correlating the U.V. spectra of substituted unsaturated ketones with their structures. Some years later, he advanced a theory on the biogenesis of the indole alkaloids (1948). Another important paper (1953) dealing with biogenesis of steroids revised an earlier hypothesis for the cyclization of squalene into lanosterol. This was followed a few years later (1956) by a scheme for the biogenesis of the macrolides which has stimulated much new research.

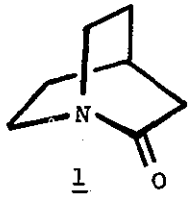
His influence has extended far beyond his laboratories in Cambridge or Basel. In conversations with visiting chemists, in seminars, and at scientific meetings, his comments and suggestions have repeatedly generated new insights into problems that

seemed hopelessly confused. A fresh, critical evaluation of experimental data by R. B. Woodward has provided the key to many a perplexing experimental or theoretical problem. From such collaborations with other colleagues have emerged, for example, the "octant rule" for assigning absolute configurations to rigid saturated ketones, based on their optical rotatory dispersion (1961). In a totally different area, Woodward's interest in the structure of iron-bis-cyclopentadienyl led him to propose the sandwich-type structure which he named ferrocene. He and his co-workers were the first to show the aromatic character of the five-membered rings.

Woodward has the rare ability to retain most of the information that he reads, and he reads the chemical literature voraciously. His students are constantly amazed at his ability to recall obscure reactions, including precise experimental conditions, which can be called into play when needed in a synthetic plan. I am sure that every co-worker can provide examples of this phenomenon. I offer two such cases from my own experience.

At the time that I began research (1941) as one of Professor Woodward's early graduate students, he was interested in the synthesis of quinine and in the chemistry of the quinuclidine system. In particular, he wished to show that 2-ketoquinuclidine (1) would not behave as an ordinary amide because of steric inhibition of resonance. Accordingly, we set out to prepare piperidine-4-acetic acid and to assay the possibility of cyclizing this amino acid to the 2-quinuclidone structure. To obtain a γ-substituted pyridine derivative as starting material

for this venture, we investigated a little-known reaction, found in the patent literature, involving the reduction of pyridine with zinc and acetic anhydride to form N-acetyl-γ-acetyldihydropyridine (2). Although this particular pyridine reduction did not play a role in Woodward's early work on quinine and quinuclidone, it was obviously a reaction which he found interesting and appealing, and he stored it in the back of his mind, to be recalled for the right occasion. This opportunity materialized eighteen years later (1959), in his bold and elegant synthesis of ellipticine (3). Here, the zinc and acetic anhydride reduction of the pyridine ring in (4) was brought forth as the key reaction in the strikingly simple 3-step synthesis of the alkaloid.



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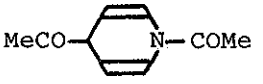

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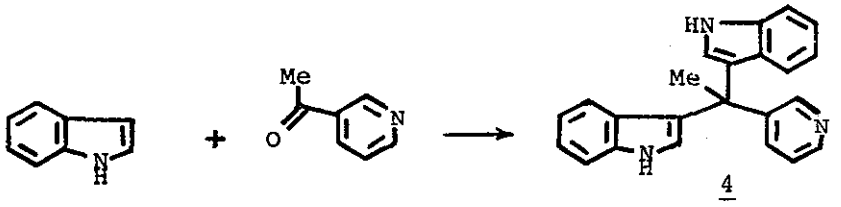

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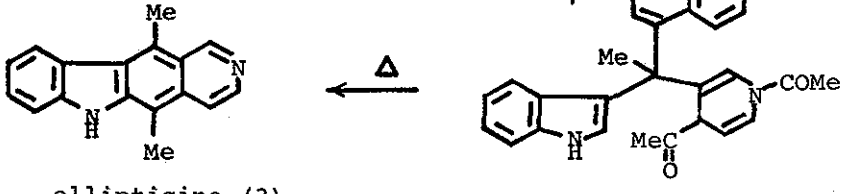
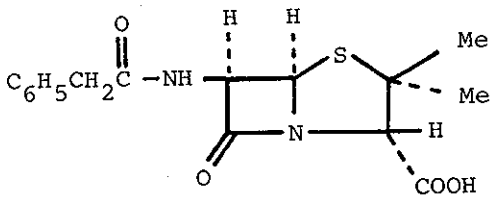


ellipticine (3)

His early ideas on steric inhibition of resonance did not have to wait eighteen years for testing. They found much quicker application in Woodward's contributions to the structure of penicillin. During the massive collaborative effort on the structure and synthesis of this antibiotic in the early 1940's, one group of investigators argued that the β-lactam structure was not compatible with the presence of a labile link in penicillin because of the observed stability of model β-lactams toward hydrolysis. It was Woodward who pointed out the important consequences of the fused-β-lactam-thiazolidine ring system in terms of steric inhibition of resonance in a hindered amide. Here again, his earlier thinking about the purely theoretical problem of amide resonance in 2-quinuclidone enabled him to make a key contribution as the principal proponent of the β-lactam structure for the penicillins.



penicillin-G

Chemistry draws Woodward to the laboratory day and night. He has tremendous vitality and physical stamina which serves him well as he works long past midnight in his office nearly every evening. His students are expected to observe the highest

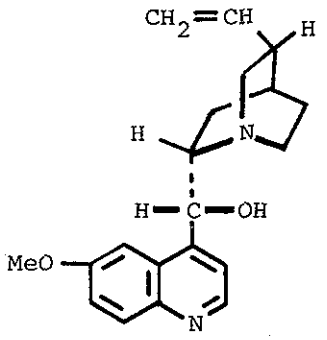
order of precision in their experimental work, and they are quickly made to realize that no amount of brilliant hypothesis or insight can take the place of hard work. In describing the field of synthetic organic chemistry, he states[2]

> It is a very demanding field, [where] one puts one's knowledge and understanding to the critical and ultimate test. One finds, for example, that there are no general reactions. And each case has to be studied, carefully, experimentally. That's the glory of chemistry--that it is an experimental science. And it will remain that for a long time to come.

Another way in which Woodward's love for chemistry is expressed is through his lectures and his presentation of seminars and colloquia. There are few scientists who can match the elegance, precision, and overall artistic quality of Woodward's talks at the blackboard. The formulas and reaction sequences are outlined in a graphic style that is nearly unique in its attention to scientific precision, clarity and aesthetics. Each presentation is in itself a dramatic and creative composition, and even the most complex phenomena are explained in a lucid manner.

Woodward's style and tastes outside of the laboratory and lecture room are well-known among his students and colleagues:[3]

> Woodward's hallmark is his plain, light blue tie; he carries the same color over to his office and (usually) his car. He thoroughly enjoys social occasions, in the limited time he allows for them. He is an accomplished raconteur. One of his favorite sports is betting on any and all topics, from science to politics to geography, again with precision and care, so that he usually wins. He reads widely in science and out of it, including fiction. He is an inveterate smoker and scorns exercise, to which he attributes many of the troubles of others.



quinine

At a young age Woodward became interested in learning more about organic compounds formed in nature and amused himself by devising syntheses for complex natural products. While he was still in high school he was working out a synthesis of quinine, and it was in the course of such self-teaching that he acquired a knowledge of organic chemical reactions that would stagger most of today's graduate students.

When he entered the Massachusetts Institute of Technology at age 16 he found the pace of the prescribed chemistry curriculum too slow for his advanced preparation; his restlessness and boredom caused him to be expelled from the Institute. Fortunately the faculty at M.I.T. recognized that in Woodward they had a unique student, and they were willing to reinstate him and to bend the rules by arranging a curriculum specially suited to him.

The following quotation from Professor James Flack Norris of M.I.T. expresses the sentiments of the Institute on the award of the Ph.D to Woodward at age 20.

> We saw we had a person who possessed a very unusual mind and we wanted to let it function at its best. If the red tape necessary for the less brilliant minds had to be cut, we let it go. We did for Woodward what we have done for no other student like him in our department. We think he will make a name for himself in the scientific world.

After receiving his doctorate from M.I.T. Woodward became an instructor of chemistry at the University of Illinois for the summer of 1937. He returned to Cambridge that fall as research assistant to E. P. Kohler. One year later he became a junior fellow of the Society of Fellows at Harvard, and in January 1941 received an instructorship in Harvard's Chemistry Department.

This was followed by an assistant professorship in 1944, an associate professorship in 1946 and then full professorship in 1950. In 1953 he became Morris Loeb Professor of Chemistry and in 1960, Donner Professor of Science.

The scientific world has bestowed recognition on R. B. Woodward in the form of honorary degrees, awards, and appointments. The following is a list of such honors as of 1977.

Honorary Doctorates

Wesleyan University, 1945; University of Manchester(England), 1954; Bucknell University, 1955; University of New Brunswick (Canada), 1956; Yale University, 1956; Harvard University, 1957; University of Southern California, 1959; University of Chicago, 1961; New England College of Pharmacy, 1961; Colby College, 1963; University of Cambridge(England), 1964; Brandeis University, 1965; University of Glasgow(Scotland), 1966; Stonehill College, 1966; University of Sheffield (England), 1966; Israel Institute of Technology(Haifa), 1966; Polytechnic Institute of Brooklyn, 1967; Eidgenössische Technische Hochschule(Switzerland), 1967; University of Western Ontario(Canada), 1968; Columbia University, 1969; Université de Louvain(Belgium), 1970; Université Pierre et Marie Curie de Paris, 1975; University of St. Andrews (Scotland), 1976; The University of London(England), 1976.

Awards

John Scott Medal [Franklin Institute and City of Philadelphia], 1945; Baekeland Medal [North Jersey Section of the American Chemical Society], 1955; Ledlie Prize [Harvard University], 1955; Research Corporation Award, 1955; Nichols Medal [New York Section of the American Chemical Society], 1956; Synthetic Organic Chemistry Award [American Chemical Society], 1957; Richards Medal (Northeastern Section of the American Chemical Society], 1958; Davy Medal [Royal Society],1959; Roger Adams Medal [American Chemical Society], 1961; Pius XI Gold Medal [Pontifical Academy of Sciences], 1961; Scientific Achievement Medal [City College Chemistry Alumni Association], 1961; Priestley Medallion [Dickinson College], 1962; Stas Medal [Société Chimique de Belgique], 1962; Gold Medal for Creative Research in Synthetic Organic Chemistry [Synthetic Organic Chemical Manufacturers Association], 1962; National Medal of Science [United States of America], 1964; Kirkwood Medal [Yale Department of Chemistry and New Haven Section of the American Chemical Society], 1965; Nobel Prize in Chemistry [Royal Swedish Academy of Sciences], 1965; Willard Gibbs Medal [Chicago Section of the American Chemical Society], 1967; Lavoisier Medal [Société Chimique de France], 1968; The Order of the Rising Sun,Second Class[His Majesty the Emperor of Japan], 1970; Hanbury Memorial Medal [The Pharmaceutical Society of Great Britain], 1970; Pierre Bruylants Medal [Université de Louvain], 1970; Scientific Achievement Award [American Medical Association], 1971; Dr. B. C. Law Gold Medal [Indian Association for the Cultivation of Science], 1972; Arthur C. Cope Award [American Chemical Society], 1973.

Other Appointments

Member of the National Academy of Sciences; Fellow of the American Academy of Arts and Sciences; Honorary Member of the German Chemical Society; Honorary Fellow of the Chemical Society; Foreign Member of The Royal Society; Honorary Member of the Royal Irish Academy; Corresponding Member of the Austrian Academy of Sciences; Member of the American Philosophical Society; Honorary Member of the Belgian Chemical Society; Honorary Member of the Harvey Society of New York; Honorary Fellow of the Indian Academy of Sciences; Honorary Member of the Swiss Chemical Society; Member of the Deutsche Academie der Naturforscher (Leopoldina); Foreign Member of the Accademia Nazionale dei Lincei;Honorary Fellow of the Weizmann Institute of Science; Honorary Member of the Pharmaceutical Society of Japan; Honorary Member of the Pharmaceutical Society of Great Britain; Honorary Fellow of the Indian Chemical Society; Honorary Life Member of the New York Academy of Sciences; Foreign Fellow of the Indian National Science Academy; Honorary Member of the Royal Institution of Great Britain; Foreign Member of the Academy of Sciences of the U.S.S.R.

References

1. A. R. Todd, New Scientist, 1965, 28, 253.

2. Proceedings of the Robert A. Welch Foundation Conferences on Chemical Research, XII. Organic Synthesis, 1969, 3.

3. P. D. Bartlett, F. H. Westheimer, and G. Büchi, Science, 1965, 150, 585.