

Robert Burns Woodward, Nobel Prize in Chemistry for 1965



During the past two decades a quiet revolution has taken place in the methods and efficiency of the chemical synthesis of organic compounds. Well-known developments in instrumentation have reduced by a large factor the effort required to obtain compounds in a high state of purity and to establish their structures. At the same time the complexity of the molecular architecture that can be constructed has increased steadily. This aspect of the revolution is due not to instrumentation but to the discovery of theoretical principles of organic chemistry and application of these principles to practical synthesis. The 1965 Nobel prize in chemistry is awarded to Robert Burns Woodward, Donner Professor of Science at Harvard University, the recognized leader of the revolution in synthesis.

The prize is awarded for Woodward's "meritorious contributions to the art of chemical synthesis." Woodward and his co-workers have completed the chain of steps required to build up, from the elements, a number of natural products, including quinine, patulin, cortisone, lysergic acid, cholesterol, strychnine, lanosterol, reserpine, colchicine, and chlorophyll. They have also worked out the molecular structures of strychnine, terramycin, aureomycin, cevine, magnamycin, tetrodotoxin, and a number of other complex natural products. The conception of these projects is characteristically Woodward's, the laboratory work is done by a large and enthusiastic group of graduate students and of postdoctoral fellows from many countries.

A list of Woodward's successes fails to convey the special character of his approach. The scope of his interest in chemistry begins to appear as one reads the structural arguments and the stratagems which led to any particular goal. It is entirely consistent with his record of original synthetic work that Woodward is also the author of more than 20 papers dealing with mechanistic and physical-organic problems. He recognized the nature of the metallic sandwich compound, ferrocene; he coined its now familiar name, and showed the aromatic character of its five-membered rings. His empirical rules concerning the ultraviolet absorption spectra of substituted conjugated systems are a widely used tool for the determination of structure. He has studied the mechanism of solvolysis in bicyclic

systems, of the dienone-phenol rearrangement, of isomerization at carbon No. 25 in steroidal sapogenins, of isoxazolium salt reactions, and of thermochromism. Interested for many years in the mechanism of the Diels-Alder reaction, he has recently collaborated with R. Hoffmann in discovering selection rules, based on quantum-mechanical considerations, for concerted cycloadditions and isomerizations that throw the light of theory on some of the remarkable stereospecificities in this field.

His originality, discernment, and cooperative spirit have brought Woodward into collaboration with colleagues in many parts of the world. A partial list of such collaborators includes D. Arigoni, D. H. R. Barton, K. Bloch, E. R. Blout, C. Djerassi, H. H. Inhoffen, O. Jeger, J. R. Johnson, W. E. Moffitt, V. Prelog, R. B. Turner, E. Wasserman, S. Winstein, and B. Witkop. Among the products of this collaboration is the much-used "octant rule" for assigning absolute configurations to rigid saturated ketones on the basis of their optical rotatory dispersions.

One of his papers dealing with biogenetic hypotheses is of special interest. Published 12 years ago from Harvard and the University of Chicago, it revised the previously proposed scheme for the cyclization of squalene into lanosterol, the metabolic precursor of cholesterol. This subject continued to be of vital interest to both Woodward and his co-author. The latter was Konrad Bloch, now a colleague at Harvard and Nobel laureate for medicine and physiology in 1964.

Woodward's wide interests in chemistry have fitted him almost uniquely for the task of synthesizing organic molecules of a complexity never before attained. Although the final structural objectives of such programs are clearly defined, the kind and sequence of chemical operations to be performed are determined by the ingenuity and style of the investigator. In addition to careful planning, Woodward's approach is often characterized by bold innovation, as in his elegant synthesis of the naturally occurring indole alkaloid ellipticine. Condensation of indole with 3-acetylpyridine gave a bisindolyl derivative (*I*) which, on reductive acetylation with zinc in acetic anhydride, was converted to a diacetyldihydropyridine (*II*). Pyrolysis of this latter intermediate yielded ellipticine (*III*). The two intermediates contain many more atoms than

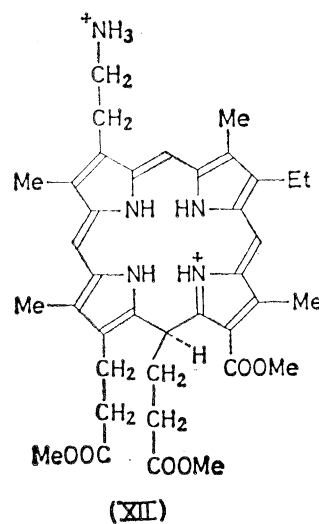
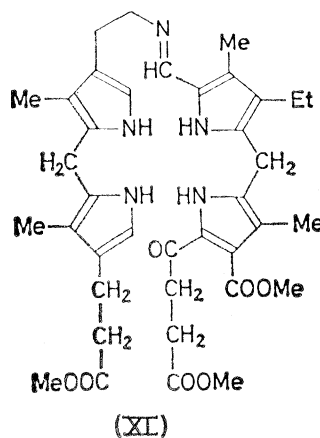
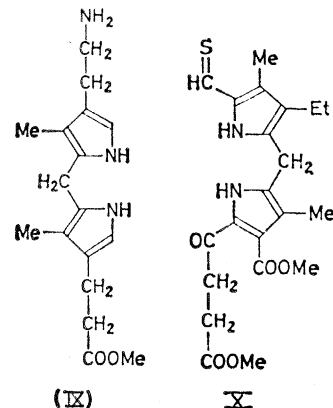
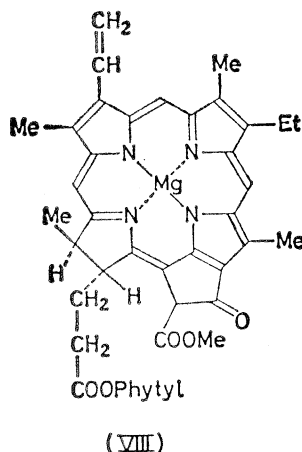
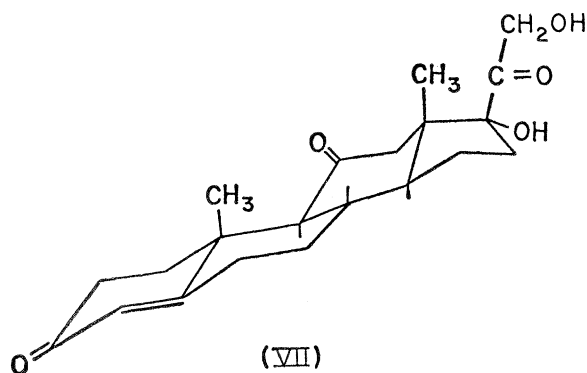
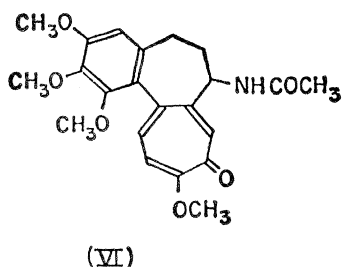
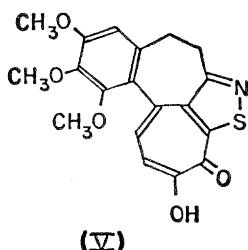
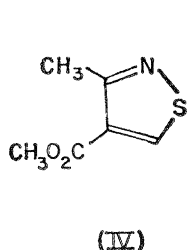
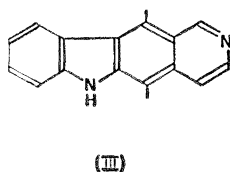
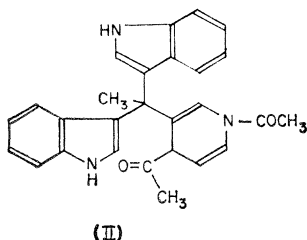
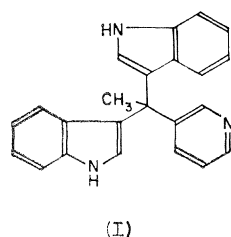
the final product, and the synthesis represents a radical departure from the often useful practice of designing a synthesis along biogenetic lines.

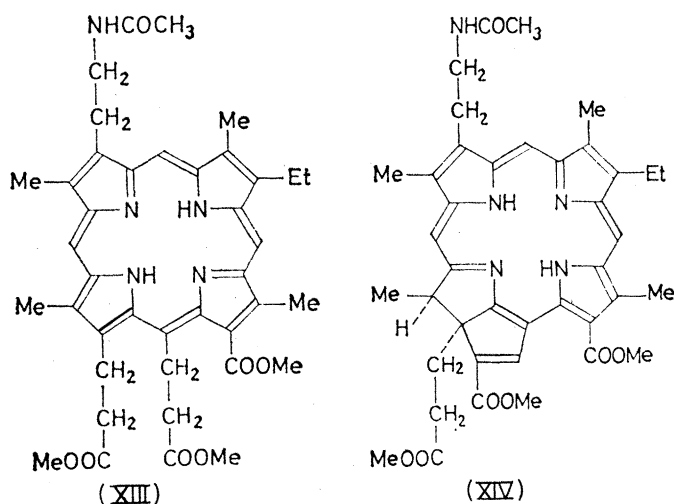
In 1963 Woodward completed a total synthesis of colchicine (VI), the toxic principle of the meadow saffron, again using a scheme for which nature provided no model. Starting with an isothiazole (IV) (a member of a class of heterocyclic compounds unknown at the time the scheme was conceived), he was able to construct a tetracyclic intermediate (V). At this stage, since the isothiazole nucleus had served its purpose, the sulfur atom was removed by reduction and the resulting tricyclic compound was converted to colchicine (VI) by standard operations. Woodward's extensive knowledge of physical-organic chemistry is manifest throughout the synthesis. The chemical properties of the isothiazoles, for example, were predicted in detail and confirmed by experiment.

The molecular frameworks of ellipticine and colchicine are not stereochemically complex, but many of the synthetic objectives first reached by Woodward were, in his own words, "exercises in stereochemistry." The hormone cortisone (VII), first synthesized in 1951, contains six asymmetric centers in its molecule. Six asymmetric centers imply 64 optically active isomers, but probably only one

exhibits the anti-inflammatory properties of the natural hormone. The critical question facing a synthetic chemist is how to avoid making a mixture of all 64 compounds. Clearly, methods are required which yield a single isomer each time a new center of asymmetry is introduced. Woodward's syntheses of cortisone, lanosterol, and reserpine have shown the feasibility of such stereospecific synthetic sequences.

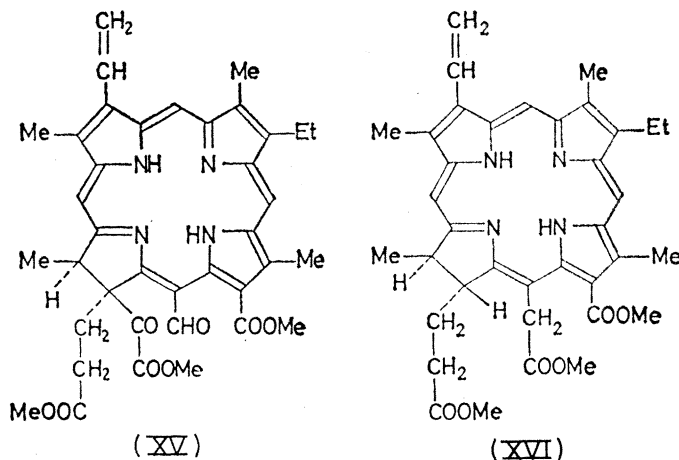
Perhaps the most brilliant of Woodward's exploits is his synthesis of the green plant pigment chlorophyll (VIII), which was completed in 1960 after 4 years of intensive effort by him and his collaborators. Chlorophyll is a highly substituted member of a class of green sub-





stances called chlorins. Unlike a porphyrin, chlorophyll does not have a fully conjugated unsaturated periphery. Less highly substituted chlorins were known to be readily oxidized to the aromatic porphyrins. Woodward reasoned that chlorophyll itself resists such oxidation because it is so highly substituted that the formation of the related porphyrin is sterically inhibited. His synthesis was constructed about the hypothesis that this steric crowding, far from introducing special difficulty into the synthesis, could be utilized as the driving force to effect the conversion of a properly substituted porphyrin to the desired chlorin. Earlier methods of porphyrin synthesis led in almost all cases to low yields of complicated mixtures, so that the structures of the substances thus obtained could seldom be assigned with certainty. The initial phases of Woodward's activities in this field were consequently devoted to a new and efficient porphyrin synthesis, which was subsequently used for the construction of the crucial intermediate. Condensation of the exceptionally sensitive dipyrromethane (IX) with the thioaldehyde (X) (the aldehyde itself, with oxygen in place of sulfur, was inert) yielded the anticipated Schiff base (XI), which, on treatment with acid, was converted into a member (XII) of a new class of pigments which were named phlorins. Oxidation with iodine followed by acetylation led cleanly and in high yield to a porphyrin (XIII) closely related to chlorophyll, and by subsequent steps to the purpurin XIV. The needed further transformations included a remarkable photochemical oxidation to produce XV; this part of the work was carried out by Woodward himself. Finally the transformation of XV to a racemic chlorin occurred readily. This chlorin was resolved into optical antipodes. One of these was identical in every respect with a degradation product of natural chlorophyll, and was readily transformed to chlorin *e*₆ trimethyl ester (XVI). This latter compound had previously been converted to chlorophyll by Willstätter and Fischer. The entire synthesis depended, as planned, on favorable steric factors.

Woodward's style is polished, showing an insight and sense of proportion that afford him strong convictions, and a well-developed dramatic sense. In the laboratory, identifications and structural assignments must be complete, spectra exact, compounds not merely pure but beautifully crystallized, or he will not accept them. His lectures,



given without notes or slides, are elegantly organized and illustrated with artistic blackboard formulas, with the key atoms shown in colored chalk. Most of the polish comes naturally to a man with such intellectual vitality, plus an incredible memory for the literature of chemistry, which he reads voraciously and rapidly. Some of the polish is the result of long hours of hard work; Woodward is in his office or laboratories 6 days and 5 nights a week, and those of his colleagues who work until midnight can still find him at his desk. Crystallization of the first synthetic sterol occurred in Woodward's laboratory on Christmas day 1950, and he and his collaborators were there to observe it.

The style goes over into other matters, too. Woodward's hallmark is his plain, light blue tie; he carries the same color over to his office and (usually) his car. Pranksters at Halloween painted his assigned parking space with "Woodward blue." 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.

Robert Woodward was born 10 April 1917, in Boston, Massachusetts. He received the B.S. degree from Massachusetts Institute of Technology in 1936, and the Ph.D. in 1937. He spent a postdoctoral year with E. P. Kohler at Harvard and was a Junior Fellow of the Society of Fellows at Harvard from 1938 until early 1941, when he joined the faculty as an instructor. He became professor of chemistry in 1950, Morris Loeb Professor in 1953, and Donner Professor of Science in 1960. He holds eleven honorary doctorates, is a member of the National Academy of Sciences, a fellow of the American Academy of Arts and Sciences, and recipient of at least ten national awards for his research, including the National Medal for Science. He is married to the former Eudoxia Muller and has three daughters and a son. The Woodwards live in Belmont, Massachusetts.

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