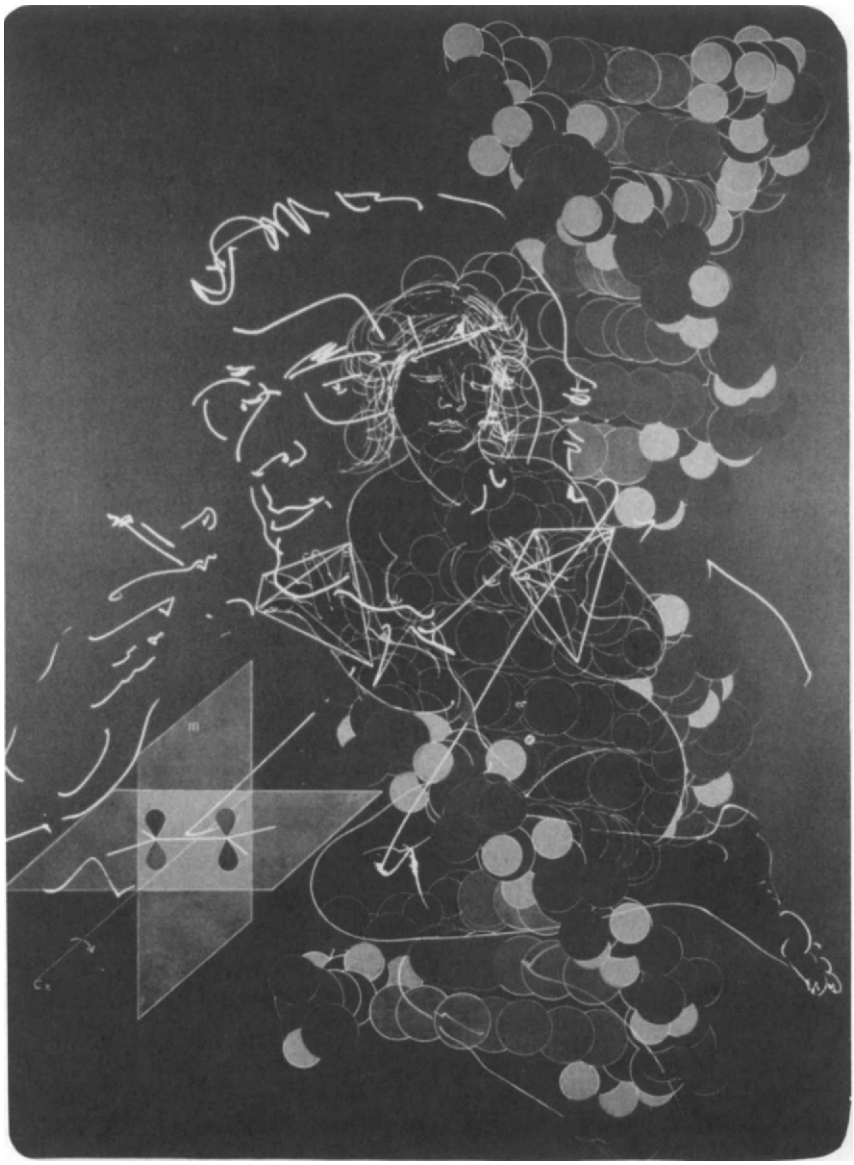

Photograph of a lithograph prepared by Hans Erni of Lucerne, Switzerland. Erni first made a painting of Woodward which he donated to the Woodward Institute of Basel, Switzerland. The lithograph was commissioned in 1977 by Professor Woodward's students and friends to celebrate his 60th birthday.

Chemistry and Biology of β-Lactam Antibiotics

Volume 1 Penicillins and Cephalosporins

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ROBERT BURNS WOODWARD

1917-1979

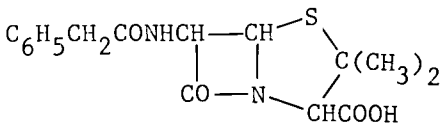
This work is dedicated to the memory of Professor Robert Burns Woodward whose untimely death occurred at the age of 62 on July 8, 1979. In many tributes Professor Woodward has been described as the greatest organic chemist of this century. There is not a scientist practicing organic chemistry whose work is not influenced or directed by Professor Woodward's many achievements toward solving problems of structural elucidation, total synthesis, biosynthesis, and reaction mechanisms. An interest in β-lactam-containing compounds was a dominant theme throughout Professor Woodward's scientific career, and in this dedication three notable achievements are singled out for brief mention.

1. Early in his scientific career, Professor Woodward recognized the synergistic power of combining the information held in various physicochemical measurements toward determining the structure of a natural product. This approach was successfully used by him starting in 1944 to unravel the many alternatives proposed for the structure of penicillin. He decided that the then novel β-lactam was indeed correct. He introduced his deductions in the volume on penicillin edited by Clark *et al.* (Woodward *et al.*, 1949) as follows:

> The subtlety of the constitutional problem presented by the penicillin molecule led to the use in the attack on the problem of almost every known applicable physical method; penicillin and the compounds derived from it probably have been studied more exhaustively from that point of view than any other class of substances. It is of especial interest that these methods not only pointed the way to a decision between alternatives which were only with difficulty differentiable on the basis of the purely chemical evidence, but ultimately provided the evidence which is generally accepted as decisive in favor of the current structure.

And later in a summarizing chapter (Johnson *et al.*, 1949), he continues:

> The extensive series of degradations which form the necessary background of any discussion of the structure of penicillin have been described in the preceding chapters, and indeed, much of the constitutional argument has been anticipated. In this summarizing chapter, we shall show how the expression [below] which has ultimately been derived accommodates all of the known facts about the chemistry of the penicillin molecule.



It should be emphasized that in almost every instance, the purely chemical work on penicillin proved susceptible to more than one plausible interpretation, and that although the now accepted formula [above] was first derived and supported on the basis of chemical arguments, it was not at first widely accepted. The physical evidence and, in particular, the magnificent X-ray crystallographic work was ultimately conclusive.

2. The course of Professor Woodward's career saw the introduction of a lecture course which was invariably entitled "Recent Advances in the Chemistry of Natural Products." This title also appeared in a 1966 *Science* article which was in fact the address in connection with the Nobel Prize in Chemistry awarded to him in 1965 for "contributions to the art of chemical synthesis." The subject of the lecture was noted by Professor Woodward in his introduction.

It gives me much pleasure to record here my gratification with the citation, which properly signalizes an exciting and significant aspect of synthetic activity. But that aspect is one which is more readily—and I dare say more effectively—exemplified and epitomized than it is articulated and summarized. Having here this morning the responsibility of delivering a lecture on a topic related to the work for which the Prize was awarded, I have chosen to present an account of an entirely new and hitherto unreported investigation which, I hope, will illuminate many facets of the spirit of contemporary work in chemical synthesis.

Cephalosporin C, a product of the metabolism of *Cephalosporium acremonium*, was isolated in 1955 by Newton and Abraham in an investigation notable for its perspicacity as well as its painstaking attention to detail.

The lecture went on to detail the brilliantly conceived total synthesis of cephalosporin C. This synthesis is described by a co-worker and long associate of Professor Woodward, Dr. Karl Heusler (1972), in an earlier volume on cephalosporins and penicillins. Many of the reactions used in this total synthesis are reported in these volumes as they are still in use for the construction of the many new nuclear analogs of cephalosporins and penicillins.

3. A third contribution to the chemistry of β-lactam antibiotics was reported by Professor Woodward in a lecture delivered at the Royal Society in London on May 2, 1979, at a meeting to commemorate the 50th anniversary of the discovery of penicillin. The lecture, entitled "Penems and Related Substances," was published posthumously in 1980 (Woodward). The synthesis of the penem ring system is detailed in this series as Chapter 5 of Volume 2 by Dr. Ivan Ernest of the Woodward