Vitamin B_{12} synthesized: A decade-long effort

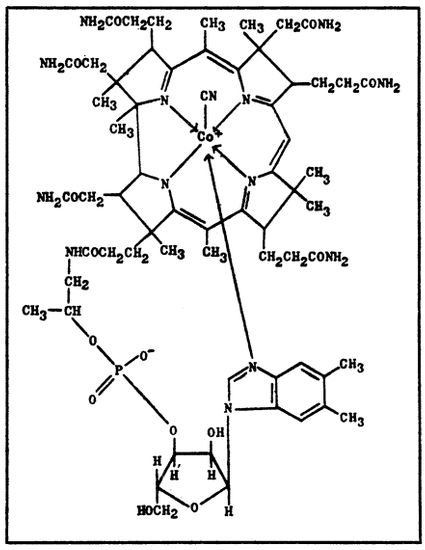
At the Boston meeting of the International Union of Pure and Applied Chemistry in the summer of 1971, hundreds of organic chemists turned out to hear Robert B. Woodward of Harvard University. Rumor had it that the Nobel laureate had finally achieved his aim of the past decade—synthesis of vitamin B_{12}. But after taking his audience through dozens of cliff-hangers, Woodward confessed he had blown the last of his material on a false hunch and would now have to start all over again.

His persistence seems to have paid off. Woodward has finally completed the synthesis. A description of the last stages of the synthesis has just been published in PURE AND APPLIED CHEMISTRY (Vol. 33, p. 145, 1973). More papers on the total synthesis will be forthcoming.

Vitamins were first discovered as essential biochemical molecules in 1905. Gradually all known vitamins were isolated and artifically duplicated by organic chemists. Vitamin B_{12} is the last to be synthesized. The second-to-last —vitamin D— was made by Woodward in the 1950's. When he turned to B_{12} in 1961, Woodward knew it would be the most difficult of the vitamins to make. Other chemists watched his efforts with awe and envy.

As an organic chemist at Princeton University puts it, "Vitamin B_{12} is an incredibly complex molecule. It challenges any organic chemist to put something that complex together." In fact, B_{12} might be considered the most elaborate natural molecule that has ever been duplicated in the laboratory. The macromolecules—proteins and nucleic acids (the reproductive molecules of cells)—are larger than B_{12}, but they are made of repeating units called polymers. Vitamin B_{12} is not. To make B_{12}, Woodward had to proceed from simple elements and compounds to still more complex compounds. B_{12}, Woodward attests, was "a monster." Building it, comments Robert Abeles of Brandeis University, was "a magnificent thing."

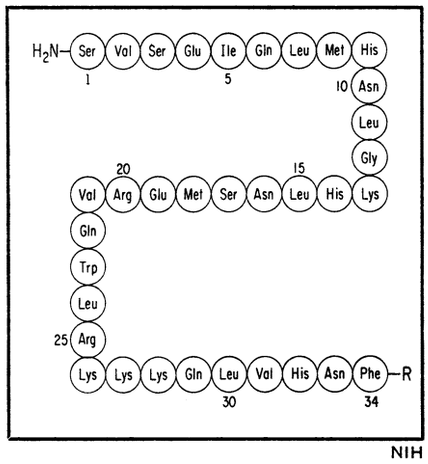
Since natural vitamin B_{12} is cheap and easily available for use in vitamin products, synthesis of B_{12} may not hold much immediate clinical value. But from the vantage of frontier organic chemistry, Woodward's synthesis has profound importance. The "fallout" of all this, he told SCIENCE NEWS, was the development of new rules of organic chemistry. These so-called "orbital symmetry" rules concern the ways



The complete vitamin B_{12} molecule.

atoms of various elements make up the chemical molecules of life. Organic chemists might eventually use these rules to make molecules that are not naturally in the human body but that may be of assistance to it. In his work, Woodward has called heavily upon the contributions of many chemists, notably Albert Eschenmoser of the Federal Institutes of Technology in Zurich, Switzerland. □

Unraveling the mysteries of parathyroid hormone



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Parathyroid's active amino acids.

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Brewer with the purified hormone.

Parathyroid hormone is released by four tiny glands near the thyroid gland in the neck. The hormone helps the body absorb calcium. H. Bryan Brewer Jr. of the National Heart and Lung Institute, in collaboration with other scientists at the NHLI, the Mayo Clinic and Ciba-Geigy Pharmaceutical Co., have now sequenced the chemical makeup of human parathyroid hormone. They have also synthesized the biologically active portion of the hormone molecule. These achievements, reported in the December PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES, should accelerate exploration of parathyroid hormone's normal activities in the human body. They should also lead to early diagnosis of diseases triggered by abnormally high parathyroid hormone levels.

Antibodies made against the biologically active portion of human parathyroid hormone, for example, might be injected into patients suspected of having too much of it in their bloodstreams.

It is not yet clear, Brewer says, whether the synthetic copy of the biologically active portion of the hormone might be used to treat deficiencies of parathyroid hormone. When such deficiencies have been diagnosed, they have responded favorably to treatments with vitamin D and calcium. Vitamin D and calcium have the advantage that they can be taken by mouth. Parathyroid can be given only by injections.

The investigators obtained the parathyroid hormone used for their efforts from human parathyroid gland tumors. So uncommon are these tumors that two years and the cooperation of 150 institutions and physicians in 12 countries were required to get hundreds of frozen tumors needed to yield adequate hormone. Active fractions of hormone were taken from the tumors by Claude Arnaud and his colleagues of the Mayo Clinic, then purified. Brewer and his colleagues at the NHLI then isolated enough of the purified hormone to determine the amino-acid sequence of the biologically active region of the hormone molecule (the first 34 of 84 amino acids). Werner Rittel and his team at Ciba-Geigy in Basel, Switzerland, strung amino acids together in the same order Brewer's group had unstrung them. This linkage comprised synthesis of the biologically active portion of the hormone. □