A New Route to Opium Derivatives

The first practical total synthesis of medically important opium derivatives was reported by Kenner C. Rice of the National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases at the recent meeting of the American Chemical Society (ACS).* Using the commercially available starting material *m*-methoxyphenylethylamine, Rice synthesized dihydrothebainone, dihydrocodeinone, and nordihydrocodeinone. These can be readily converted to morphine, codeine, and thebaine with the use of techniques developed in 1976 by Henry Rapoport and D. D. Weller of the University of California at Berkeley. Rice has synthesized both the naturally occurring forms of the drugs and the mirror-image forms.

At least eight other groups had previously synthesized morphine or its derivatives, but none of these expensive and time-consuming processes was of practical value. The synthesis is of great interest because of U.S. reliance on imported opium poppies and straw for the estimated 55,000 kilograms of medically prescribed codeine (16 doses of 15 milligrams each for every man, woman, and child) and the smaller quantity of related drugs used in the United States each year. A shortage from 1973 to 1975 forced the government to release about half its strategic reserves of opium to commercial processors. The mirror-image forms are also of interest because they can be used to unravel the nature of opiate receptors as well as to study nonspecific effects on the central nervous system.

In the synthesis, *m*-methoxyphenylethylamine is reacted with 3-hydroxy-4-methoxyphenylacetic acid to form a racemic mixture of tetrahydroisoquinolines. These enantiomers can be separated as tartrate salts to provide optically pure precursors of the naturally occurring and mirror-image compounds. The key step in the synthesis is the subsequent "directed Grewe cyclization" of the derivatized isoquinoline to form the appropriate carbon-nitrogen skeleton of the alkaloid. This step has been unsuccessfully attempted by other investigators using different intermediates. Rice was successful, he says, because he used a readily removable bromine atom to block an undesirable cyclization and because he used trifluoromethanesulfonic acid as a catalyst. The cyclization product can then be converted to any of the three previously mentioned intermediates. Natural codeine can be synthesized from the starting material with only six isolated intermediates and with an overall yield of 15 percent. Yields and number of steps in the synthesis of the other products are comparable.

Frank I. Carroll, George A. Brine, and Anita H. Lewin of the Research Triangle Institute are now using Rice's technique to produce substantial quantities of the mirror-image forms of the drugs under a contract from the National Institute on Drug Abuse. These will then be made available to qualified investigators for studies of opiate receptors and effects.

Accelerating the Synthesis of DNA

New reagents and a new solid support can greatly speed the synthesis of polynucleotides, according to Steven P. Adams and Gerald R. Galluppi of Monsanto Company in St. Louis. The key to increased speed and reactivity, Adams told the ACS meeting, is the use of a "long chain alkylamine controlled-pore glass" produced by Pierce Chemical Company of Rockford, Illinois. The glass beads are covered with glycerol to which is attached an alkylamine through a carbamate linkage. The 3′-hydroxyl of the initial nucleoside is attached to the amine as a succinate ester. The net effect is that the nucleoside is attached to the support through a molecular chain containing 21 atoms, thereby relieving steric inhibition of nucleoside addition.

Subsequent nucleosides are added to the growing chain as diethyl or diisopropyl phosphites rather than as the conventional phosphate esters. Adams says the phosphites are stable in solution at least ten times as long as the conventional reagents, but react faster. Dichloroacetic acid is used to remove the protective group on the 5′-hydroxyl; it performs this function in less than 1 minute while catalyzing a minimal amount of depurination. The complete cycle time for adding one nucleoside to the growing chain is about 12 minutes, compared to the 90 to 120 minutes now required on automated equipment.

Each step in the reaction chain proceeds in high yield, says Adams, so that polynucleotides containing 20 bases can routinely be made in 45 to 50 percent yield. Adams and Galluppi recently made a 51-base polymer—the longest polynucleotide synthesized to date—in only 10 hours with an overall yield of 5 percent. The polynucleotide was a probe for bovine growth hormone. They performed the reactions manually, but Adams says the technique could readily be adapted for automation.

A New Approach to Nonnutritive Sweeteners

A sucrose compound that has the full sweetness of sugar, but that cannot be used by cariogenic (cavity-producing) bacteria and that cannot be absorbed through the walls of the gastrointestinal tract, was reported at the ACS meeting by Arthur M. Usmani and Ival O. Salyer of the University of Dayton. The sweetener, which they call polysugar, is formed by connecting natural sucrose through an ether linkage to a polymer of vinyl alcohol. The sugar moiety can interact with taste buds, but the polymer is too large to be absorbed and too stable to be digested.

A similar approach to food additives has been taken by other investigators, particularly the Dynapol Company of Palo Alto. Dynapol has an antioxidant which is based on the same principle and is under review by the Food and Drug Administration. The company has also worked on a red food coloring and a sweetener, although trouble arose with the sweetener because of taste problems. In any case, the company is now being liquidated because of the withdrawal of one of its major investors.

Usmani and Salyer found that the taste of polysugar is highly dependent on the ratio of sucrose molecules to vinyl alcohol molecules. Too little su-

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*183rd National Meeting of the American Chemical Society, 28 March to 2 April 1982, Las Vegas, Nevada.

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crose resulted in a product that was not sweet; too much and it was bitter. Polysugar is resistant to both boiling water and boiling dilute hydrochloric acid, and thus should be inert in the gastrointestinal system. The two investigators hope to begin work with animals soon in order to establish the safety of the product.

Conductive Polymers Set for a Breakthrough

Electrically conductive polymers may find wide use during the next few years in batteries, power transmission cables, and electrical shielding, among other applications, judging from a week-long symposium at the ACS meeting. Use of these materials could total at least 700 million pounds at the end of this decade provided that certain technical problems can be solved, according to Jeffrey R. Ellis of Princeton Polymer Laboratories, Inc., and R. S. Schotland of Schotland Business Research, Inc., of Princeton. Privately funded work is proceeding rapidly in this country, and in Japan the government recently initiated a $25-million program of research at five companies.

The most important conductive polymers available now generally have conjugated double bond systems. Among them are polyacetylene, discovered by Alan G. MacDiarmid and Alan J. Heeger of the University of Pennsylvania; polyparaphenylene, discovered at Allied Chemical Corporation in Morristown, New Jersey, by a group headed by Ray H. Baughman; and polyparaphenylene sulfide, discovered independently by Allied and a group at the IBM Research Laboratories in San Jose, California, headed by G. Bryan Street.

These materials are insulators when pure, but they become conductors when doped with either electron donors such as alkali metal ions and iodine or electron acceptors such as arsenic pentafluoride. Their conductivities can become as good as that of mercury, or about one-hundredth that of copper. Conductivity is believed to be mediated by solitons—stabilized carbonium ions and carbanions with unique delocalized structures.

Polyacetylene is formed in thin silvery foils that make good electrodes for batteries, says MacDiarmid. Their chief advantage is that discharge involves migration of the dopant into the electrolyte solution rather than dissolution of the electrode, as occurs in conventional batteries. They thus can be recycled a large number of times without significant degradation. Batteries produced with currently available materials have an energy storage density comparable to that of a lead-acid automobile battery, but can deliver 20 to 25 times the current. Polymer-based batteries could thus be ideal for electric-powered automobiles. Stretching the polyacetylene foil aligns the fibers of which it is composed so that the polymer conducts electricity in one direction preferentially. It might thus be possible to produce self-insulating conductors.


Plastic powered?

Polymer-based batteries might be ideal for electric automobiles such as this prototype developed by General Electric and Chrysler.

The chief problem now is the environmental stability of the polymers, which are particularly sensitive to water vapor in the atmosphere. Environmental stability can be improved by encasing the polymers in other plastics, but this obviously adds to the cost. Gary E. Wnek and Mary E. Galvin of the Massachusetts Institute of Technology reported the polymerization of acetylene within a matrix of solid low-density polyethylene. The materials produced in this fashion had a greater environmental stability but lower conductivity.

A final problem with the polymers is that they are not very workable. Polyacetylene is insoluble and infusible. Polyparaphenylene can be processed only by sintering, while polyparaphenylene sulfide can be melt-processed. For conductive polymers to reach their full potential, therefore, it seems likely that new compounds will have to be developed that are both more workable and more stable.

New Drugs for Parkinson's, Cancer

A promising new drug for Parkinson's disease is under study by Krishnaswamy S. Rajan and S. Mainer of IIT Research Institute in Chicago. Parkinson's disease is normally treated with levodopa, which replenishes the brain's dopamine supply. Levodopa is rapidly decarboxylated by enzymes in the liver and gastrointestinal tract, however, and large doses must be given to ensure that adequate quantities reach the brain. Another approach is to combine levodopa with carbidopa, which inhibits the enzyme action and allows more drug to reach the brain. Over a long period, both levodopa and the combination produce undesirable side effects, including nausea, tremors, and psychosis.

Working with investigators at the Medical College of Augusta and the Illinois State Psychiatric Institute, Rajan and Mainer have found that decarboxylation can be inhibited by administering levodopa as a chelate of copper or zinc. Tests in animals show that the chelate delivers higher concentrations of drug to the brain without toxicity and does not produce tremors.

On another front, Barnett Rosenberg of Michigan State University, one of the original developers of the widely used anticancer drug cisplatin [*cis*-diamminedichloroplatinum (II)], and his colleague Devinder S. Gill reported that a palladium analog of cisplatin may be effective against intestinal tumors that are resistant to cisplatin. Cisplatin works against tumors only after the chlorine ligands have been replaced by water in situ. The intestinal tract contains such high concentrations of chlorides that this exchange does not occur and cisplatin is inactive.

Rosenberg had hoped that substituting palladium for platinum would overcome this problem, but it did not. Substituting nitrate ligands for the chlorine in the palladium compounds, however, made the drug very effective against intestinal tumors in mice. Rosenberg and Gill have subsequently made the platinum-nitrate analog, but this is not as effective as the palladium compound. The palladium compound also appears to have fewer side effects.

—Thomas H. Maugh II—