CHEMISTRY

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Palladium: Metal contra-cancer

From the same university laboratory that developed cisplatin — the widely used, platinum-based anticancer drug — comes a new set of drugs that may effectively combat a wider range of the cancer spectrum and cause fewer harmful side effects. Developed by Devinder S. Gill and Barnett Rosenberg of Michigan State University in East Lansing, the new drugs contain a palladium (Pd) nitrate (NO_3) complex instead of the platinum (Pt) chloride (Cl) combination in cisplatin.

Now marketed by Bristol Laboratories as Platinol, cisplatin was discovered and developed by Rosenberg and colleagues in the late 1960s. Clinical trials of this platinum chloride anticancer drug began shortly thereafter. In 1978, the U.S. Food and Drug Administration approved it for use against cancers of the testicles and of the ovaries, and earlier this year cisplatin was approved for use against advanced bladder cancers. In addition, a growing body of research indicates that cisplatin may be an effective battler of lung cancer.

But because of its modus operandi, cisplatin cannot attack the various gastrointestinal cancers, including those of the stomach and colon. In order for cisplatin to do its job when it enters a cell, it first must lose its chloride ions and then fill the resulting empty spaces with water molecules. In most cells, the transformation from the chloride to the aquated, active form proceeds smoothly. However, the cells of the intestinal tract already contain a high concentration of chloride ions — a chemistry that discourages the chloride ions on cisplatin from leaving their parent compound. Consequently, "in the intestinal tract, cisplatin goes in and comes out and nothing happens," Gill says.

But "the chemistry of the palladium complexes is different," the researcher continues. He and colleagues believe that the nitrate on the complex — the portion of the molecule corresponding to cisplatin's chloride — will leave the parent compound even amid high cellular concentrations of chloride. Moreover, animal tests indicate that the new palladium compounds not only demonstrate an anticancer activity at least comparable to that of cisplatin, but also show less toxicity than the platinum chloride formulations, which can cause nausea, vomiting and kidney damage. Still, Gill and Rosenberg are quick to point out, years of clinical experiments must be conducted before the new palladium-based anticancer drugs are fully evaluated.

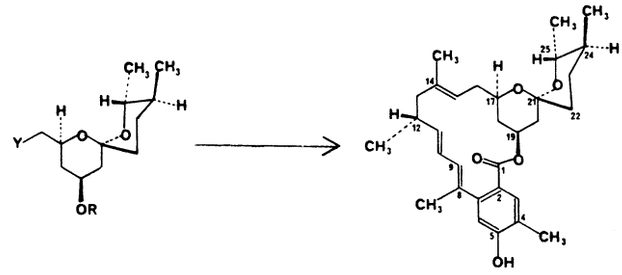
The milbemycin story

A naturally occurring chemical that is extraordinarily potent against certain agricultural pests and parasites now has been synthesized — times two. Both Amos B. Smith III of the University of Pennsylvania at Philadelphia and David R. Williams at Indiana University in Bloomington have, along with their respective colleagues, independently achieved the only total synthesis of milbemycin β_3.

First reported discovered in 1975 by Japanese researchers, the milbemycins constitute a family of antibiotics produced by a *Streptomyces* bacterium. Scientists soon found that these chemicals actually are relatively weak antibiotics — substances produced by microbes to protect their growth zones from other microbes — but that they are potent pesticides and parasiticides, Williams says. Furthermore, the milbemycins are highly specific agents — that is, they fight pests such as mites, aphids, intestinal worms and tent caterpillars but cause little harm to the plants and animals they are protecting.

To date, 13 members of the milbemycin family have been identified. Structurally speaking, milbemycin β_3 is one of the simpler members of that clan, so Smith and Williams decided to tackle its synthesis. Both researchers treated the target molecule as a sort of jigsaw puzzle composed of separate pieces — including a spiroketal component (see the diagram below), for example — that could be synthesized separately and then assembled. But Smith and Williams each divided milbemycin β_3 into different pieces, resulting in slightly dissimilar end results. Specifically, the end product of Williams's synthesis is the desired synthetic correlate of the naturally occurring form of milbemycin β_3; Smith's synthesis, on the other hand, ends with both the desired product and its mirror image. The researchers independently have submitted their synthetic routes to the JOURNAL OF THE AMERICAN CHEMICAL SOCIETY for publication.

The completed syntheses are making possible "a deeper understanding of the chemistry of milbemycins," Williams says. The drive to learn more about such chemicals, he says, is indicative of the new era in pesticide chemistry. "Before, in the [agricultural chemicals] industry, the basic thinking ... was, 'It doesn't matter how toxic these substances are as long as they are cheap; we can sacrifice safety as long as they're pennies per pound.'" But that philosophy "caused problems," says Williams, "because it led to our use of chemicals such as DDT." By contrast, says Williams, "the milbemycins give us what I would call 'fine chemicals' — things you can't make for pennies per pound, but because they work safely in such small amounts and with such high specificity in a wide variety of applications, they might be economical in the long run."



A spiroketal — Milbemycin β_3

Making shale oil more attractive

Complex, expensive processes required to upgrade unconventional petroleum sources long have precluded them from being attractive energy alternatives. Now, however, researchers at Amoco Oil Co. in Naperville, Ill., have developed, on an experimental scale, a relatively simple technique that produces a major petroleum product from an unconventional source.

A. Martin Tait and Albert L. Hensley Jr. have developed special catalysts — substances that accelerate chemical reactions without undergoing change themselves — that appear to convert whole shale oil into jet fuel in a single step. The Amoco catalysts are mixtures of cobalt, molybdenum and chromium oxides on an alumina support. The new substances not only aid in the removal of the nitrogen (which can cause engine "knocking" and fuel deterioration during storage) and sulfur contaminants, but also survive the high-temperature cracking of the waxy, long-chain shale oil molecules into the desired shorter-chained compounds. Conventional petroleum technology accomplishes these tasks in the more complicated multistep refining processes.

Shale oil is just one of several unconventional sources of petroleum that lie in U.S. reserves estimated to be more than four times the size of the conventional oil reserves, Tait and Hensley report. If efficient means could be developed to convert those raw materials to useable petroleum products, they could provide a U.S. supply for an estimated 100 years at the current rate of consumption, the researchers say.