Chemistry

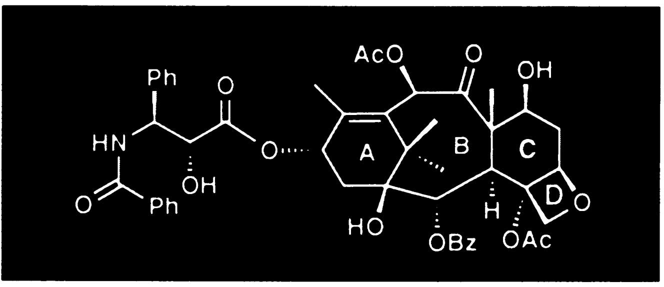
A photo finish for total taxol synthesis

Taxol – the complex anticancer compound derived from the bark of the Pacific yew tree, *Taxus brevifolia* – has finally yielded to the ingenuity of two chemistry research teams.

Both report that they've figured out how to make this drug in a laboratory without having to fell the precious evergreens.

Kyriacou C. Nicolaou, a chemist at the Scripps Research Institute in La Jolla, Calif., and his colleagues reported the "total synthesis of taxol" in the Feb. 17 Nature. Robert A. Holton, a chemist at Florida State University in Tallahassee, published his recipe for taxol in the Feb. 23 Journal of the American Chemical Society, based on results obtained in December 1993.

The two teams finished neck and neck after a 10-year race involving more than 30 research teams worldwide to make a test-tube version of this unusually intricate natural compound.



NATURE

The taxol molecule.

Identified in 1964 and analyzed structurally in 1971, taxol has revealed itself as a promising antitumor agent for ovarian, breast, lung, and skin (melanoma) cancers. Tests of taxol's safety for use by patients began in 1983. In 1992, the Food and Drug Administration approved it for treating ovarian cancer.

Yet the limited supply of natural taxol has hamstrung research and treatment efforts. In the early days of taxol research, all of the bark from a single 40-foot-tall, 100-year-old tree yielded one scant 300-milligram dose of the drug – killing trees on a scale that made environmentalists apoplectic. The recent discovery of ways to extract taxol from European yew needles *(Taxus baccata)*, a yew fungus *(Taxomyces andreanae)*, and *Taxus* bushes have eased supply pressures.

Still, scientists must be able to synthesize taxol before they can make other, related antitumor agents. Taxol's unique structure – a diterpenoid compound with a core taxane ring, a rare four-membered oxetane ring, and an ester side chain – pointed toward a previously unrecognized anticancer mechanism. Now chemists may tinker with the taxane ring and possibly improve it.

The two teams took somewhat different approaches to the synthesis. Nicolaou's group worked out a way to join two big chemical rings together, forging a third in the process. The chemical sequence involves more than 28 steps. Holton's group tried another tack. Since Taxol has two main components – a large, naturally extractable chunk, called baccatin III, hooked to a snowflakelike tail of 34 atoms – the Tallahassee chemists focused on the troublesome tail. They then figured out how to bind the two pieces together, curtailing a total synthesis that involves nearly 40 chemical steps.

But this whirlwind of work may bear future pharmacological fruit. Maybe chemists can tweak taxol into a more potent form with fewer side effects, diminishing patients' adverse sensitivity reactions. A drug that dissolves in water – taxol doesn't – would ease treatment, too, as would a related drug to combat some tumors' resistance to taxol's cancer-fighting mechanisms.

Indeed, another generation of designer "taxoids" may, in the end, give rise to a preferred anticancer drug.

Physics

Ivars Peterson reports from Pittsburgh at an American Physical Society meeting

Getting order out of a mixture

Shaking up a can of mixed nuts tends to bring the larger nuts to the top, while the smaller ones settle to the bottom (SN: 6/26/93, p.405). However, until recently, researchers had little reason to suspect that similar segregation effects sometimes occur without shaking in a mixture of tiny, different-sized particles suspended in a liquid. Particles would simply wander randomly throughout the liquid without separating into regions dominated by particles of a certain size, they believed.

New experimental results show that for mixtures of two different sizes of spheres in salt water, segregation can occur for certain size ratios, concentrations, and proportions of the two components. Although such a mixture starts out distributed uniformly throughout a container, some of the large spheres eventually end up packed against the container's walls. These large spheres settle into patterns more typical of a crystal than a disordered material. Arjun G. Yodh, Anthony D. Dinsmore, and their coworkers at the University of Pennsylvania in Philadelphia and the Exxon Research and Engineering Co. in Annandale, N.J., performed the experiments using spheres ranging in diameter from 46 to 460 nanometers.

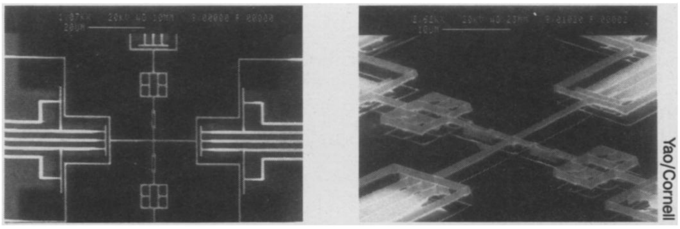
At first glance, this finding seems surprising because the amount of disorder (or entropy) in the mixture appears to decrease spontaneously. However, although some of the large spheres collect together into neat arrays at the container's walls, this leaves a larger volume within which the small spheres can move freely in the middle of the container. This extra motion makes up for the increased order among the large spheres. In the experiments, small spheres outnumber large spheres by a factor of as much as 1,000.

"We have the paradoxical effect that we have an increase in entropy when we have an ordering of the large particles," Dinsmore says. "It's an important effect under the right conditions." The researchers suggest that this type of ordering may prove relevant in the behavior of paints and other mixtures.

Vibes for a silicon microclock

Tap a tuning fork and it vibrates at a characteristic frequency. A microscopic, suspended sliver of silicon, activated by a brief electrical pulse, also vibrates, though at a much higher frequency. Built into a silicon chip, such a tiny "resonator" may someday serve as a simple electromechanical clock for electronic circuits or even as the basis for a miniaturized scanning tunneling microscope.

J. Jason Yao, now at the Rockwell International Corp. Science Center in Thousand Oaks, Calif., and his coworkers at Cornell University have fabricated such resonators out of single crystals of silicon. In the example shown, a cross-shaped structure suspended over a silicon surface vibrates at a precise frequency. It's also possible to change this characteristic frequency by applying a voltage to the structure.



Yao/Cornell

This pair of scanning electron microscope images shows the top view (left) and a tilted view (right) of a tunable silicon resonator that vibrates at about 1 megahertz. Suspended from four silicon slabs, the x-shaped resonator can vibrate sideways or up and down above the surface. The entire device is just a few micrometers wide.