

NCL develops safe route to carbamate pesticides

The Bhopal disaster of December 1984 in which more than 3000 people died was the result of the escape of large volumes of stored methyl isocyanate (MIC) into the atmosphere. At Union Carbide's pesticide plant in Bhopal, MIC was reacted with 1-naphthol to produce the pesticide carbaryl. Since the disaster production of carbamate pesticides by this process has been prohibited in India. An earlier process for the same group of pesticides used phosgene instead of MIC; phosgene was first reacted with the appropriate phenol or naphthol and the resultant aryl chloroformate treated with methylamine to form the carbamate. However, environmentalists throughout the world view the large-scale use of phosgene with extreme mistrust because of its toxicity and corrosive nature.

Since December 1984, the National Chemical Laboratory (NCL) in Pune has been deeply involved with the problems associated with such carbamates—first in analysing the causes of the Bhopal accident and later in evolving environmentally more acceptable processes for their manufacture. This was especially important because carbamate pesticides in general, and carbaryl in particular, are extremely useful for protecting crops such as cotton, paddy, sugarcane and vegetables; they are also biodegradable and have relatively low mammalian toxicity.

In a joint effort at NCL a chemical engineering group under R. V. Chaudhari and an organic chemistry group under S. Rajappa have succeeded in developing a new process for the entire range of car-

bamate pesticides; this route does not use either MIC or phosgene. The strategy involves the use of carbon monoxide as the source of the carbonyl group in the carbamate molecule. The process consists of two steps, an oxycarbonylation, followed by a transesterification reaction. The chemical engineering group, which includes A. A. Kelkar, S. P. Gupte, D. H. Kolhe and V. S. Venkatesan, developed the oxycarbonylation step, in which the salient features are (i) the use of a novel catalyst to bring about the reaction of methylamine with a mixture of carbon monoxide, oxygen and methanol, (ii) multiphase contacting, and (iii) high-pressure engineering. The product of this oxycarbonylation step is methyl *N*-methylcarbamate. The next step in the projected route was the conversion of the alkyl carbamate into an aryl carbamate—a transesterification. Such a transesterification by conventional methods is a reversible reaction in which the equilibrium lies far towards the alkyl carbamate (starting material). More than fifty experiments only served to confirm this dismal fact. This was indeed the crux of the problem.

The organic chemistry team therefore had to devise a totally new reaction to overcome this obstacle. In discussion with G. H. Kulkarni and R. H. Naik, the two organic chemists on the team, one of the ideas proposed was to transform the reaction into an irreversible one. Phosphorus oxychloride was identified as the reagent that might do the trick. Reaction of methyl *N*-methylcarbamate with phosphorus oxychloride and 1-naphthol led to

an excellent yield of the desired 1-naphthyl *N*-methylcarbamate (carbaryl). The success of the reaction was due to the cleavage of the bond between the methyl group and oxygen by means of the counterion (chloride). Proof of this was subsequently provided by the isolation and identification of the liberated alkyl chloride.

This is the first time that carbamate pesticides (such as carbaryl) have been synthesized by the oxycarbonylation/transesterification route and nowhere in the world is such a process being followed. Steps to commercialize the process are already being taken by Excel Industries, Bombay, and pilot-plant trials are expected to begin soon. Excel supported the research at NCL even at the stage when experimentation on the new idea had not been started. Commercial production of carbaryl is expected to begin around 1992–93. The demand for carbaryl in the country is around 2000 tonnes per year; there is also good export potential.

The oxycarbonylation route is also applicable in the synthesis of several other industrially important chemicals, which are otherwise synthesized by a phosgenation route. NCL is already active in developing nonphosgene-route processes for other carbamate derivatives, isocyanates, polycarbonates and urea derivatives. It is the general policy of NCL to develop nonhazardous and environmentally safe processes.

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Physics taught with a difference

Principles of Technology (PT) is an innovative attempt to solve a big problem—the lack of technical training in the US work force. Marcia Barinaga writes in *Science* that, by teaching principles of physics rather than simply teaching techniques for auto repair or metalworking, the course's developers hope to provide students with the skills needed to adapt to a rapidly changing and increasingly technical workplace. PT is directed at the

middle 50% of high school students who are not bound for a 4-year college and who, for the most part, will head from high school straight to the workplace.

Developed in the mid-eighties, the 14-unit, 2-year course is now being taught to 40,000 students in 1500 US high schools. It emphasizes hands-on laboratory exercises and supplements them with videos. PT covers the concepts of force, work, rate, resistance, energy, and power and

their applications in fluid, mechanical, electrical and thermal systems.

Through the efforts of physics teachers who also teach PT, physics is being made relevant to the lives of students. Many say they see positive effects already.

Critics of PT complain that, in its effort to demystify physics, it is bungling physical concepts and turning out graduates ill equipped to communicate

with the rest of the physics and engineering world. Another critic faults the course for providing little sense of the importance of experiments in science. Yet another critic complains that the PT

course material spoon-feeds mathematics to the students. But defenders of PT say the course has different goals than a college physics course because its students have different needs. PT's mission, they

say, is to instill the concepts essential in the technological workplace—not to stimulate the abstract thinking needed in academic science.

RU 486 and the abortion debate

Debate and arguments are raging over whether or not to license RU 486 for use. But there is one thing no one argues about—RU 486 taken in conjunction with prostaglandins is an extremely effective method of terminating pregnancy within the first 9 weeks of gestation.

The way the pill works

In women, the steroid hormone progesterone plays a central role in the establishment and the maintenance of pregnancy. In the preparation process known as decidualization, the womb lining becomes thicker and blood supply to it increases. Progesterone acts on target cells by way of the progesterone receptor, a hormone-binding protein, obligatorily involved in the target cells response. RU 486 is also a steroid with a high affinity for the progesterone receptor. It is the first available active antiprogesterone. When RU 486 enters the target cells, it blocks the binding of progesterone to its receptor by itself binding to the receptor. The sequence of events that follow normal activation by progesterone are prevented and maintenance of pregnancy fails.

The debate

According to Joseph Palca in *Science*, the development of RU 486 is a case study in how biomedical research and public policy occasionally collide. Groups opposed to abortion called RU 486 the 'death pill' and they have been largely responsible not only for keeping the drug out of the US, but also for intimidating researchers interested in exploring the myriad potential medical uses for the drug.

The significance of RU 486 for developed countries is not that it is measurably safer or more effective but that it can be used in relative privacy. It is therefore not surprising that RU 486 is viewed with alarm by antiabortion

groups. In France, approximately 25,000 have chosen RU 486 over surgery for abortion in 11 months since the government decreed that it be made available on an experimental basis.

So far, France is the only country in which RU 486 is widely available, due to the reluctance of the manufacturer to permit sale of the drug anywhere else. The sluggishness with which RU 486 is being brought to the market around the world is also a source of immense frustration to its chief developer, Etienne-Emile Baulieu, one of France's leading scientists. Baulieu developed RU 486 in the late seventies while he was consultant to the French pharmaceutical company Roussel-Uclaf, a subsidiary of the giant German company Hoechst AG. Although the French government has agreed with Baulieu that women should have access to his drug, RU 486's road to market has been anything but smooth. In France the abortion debate has not been without passion. Antiabortionists and Catholic hospitals served notice that they would stop buying any product made by Hoechst or its international subsidiaries if the company continued to market RU 486. On the other hand, doctors at the World Congress of Obstetrics and Gynecology meeting two years ago also threatened to boycott Hoechst products if the company did not make the drug available. Many countries have completed the tests necessary for licensing RU 486, but Roussel's parent Hoechst has been unwilling to

market the drug outside France.

The treatment consists of three 200-mg pills of RU 486, followed 48 hours later by a small amount of prostaglandin, either as an injection or a pessary. RU 486 blocks the normal action of progesterone on the cells lining the uterus to accept and sustain an embryo through development and the prostaglandin helps encourage the womb to contract and expel its contents. Approximately 96% of women receiving the two drugs within the first 9 weeks of conception have a complete abortion within a day of receiving the prostaglandin.

One cannot ignore the potential for misuse. This will not be limited just to pills obtained on the black market. If the drug does become legally available by prescription from pharmacies it is probably inevitable that it will be improperly used. Opponents of RU 486 worry that the drug will be used indiscriminately in developing countries. Some say that in their rush to terminate pregnancy, supporters of RU 486 are ignoring the health of the mother. But a supporter says, 'Any medical approach to termination of early pregnancy, like an approach involving one of these antiprogestins, will always require backup from surgical facilities.'

RU 486 future and potential

Potential applications of RU 486 are in the treatment of patients with Cushing's syndrome, a condition caused by excess production of cortisone; in basic research

