NEW CHEMISTRIES IN CROP PROTECTION

Hamish Kidd reports on a recent meeting dedicated to the memory of John Dingwall of Novartis who sadly died in February 2000.

Introduction

A meeting organised by the BioActive Substances and Crop Protection Groups of SCI was held on 19 June 2000 at the SCI headquarters in London. The meeting was dedicated to the memory of the late John Dingwall of Novartis, whose idea the meeting was, and who was involved in the initial organisation. The meeting started with an appreciation of John given by Robert Nyfeler, a colleague from Novartis. The meeting, as implied from the title, was very chemically based, giving detailed information on the synthetic methods involved in the development of a wide range of crop protection chemicals, most of them already launched at Brighton or other recent conferences. This meeting was intended to give companies the opportunity to describe the chemistry behind their molecules in more detail. In most cases there was an initial chemical discovery, often as a result of a screening programme, followed by SAR studies and biological trials to optimise biological activity; in almost all cases this process was spread over a period of some 20 years.

The meeting was split into two sessions, one dealing with herbicides and the other with insecticides and fungicides (in fact there was only one of the latter).

Herbicides

BAS 625H

U Misslitz from BASF spoke about BAS 625H, which is a cyclohexanedione interfering with lipid biosynthesis. Over the last 20 years several members of this class (e.g. cycloxydim) have been introduced into the market as graminicides for use in broadleaf crops – so called “first generation cyclohexanodiones”. BAS 625H has been termed a “second generation cyclohexanodione”, being capable of grass weed control on monocotyledonous crops like maize, rice or small grain cereals at low application rates. Dr Misslitz described the synthesis of the molecule by condensation of cycloxydim with a moderating hydroxylamines to give the oximethers. Over 2000 compounds were synthesised in the search for the most active molecule with acceptable selectivity. For more information on BAS 625H see Proceedings of the 1999 Brighton Conference – Weeds, 1, 65.

Isoxaflutole

Ken Pallett of Aventis CropScience described the development of this isoxaflutole (IFT) for preemergence control of broadleaf and grass weeds in maize and sugarcane. The first isoxazole lead was synthesised in 1989 and isoxaflutole synthesised in 1991. The biochemical target of IFT is p-hydroxyphenylpyruvate dioxygenase (HPPD), a component of the biochemical pathway that converts tyrosine to plastoquinone. IFT is a pro-herbicide, since it is actually the diketonitrile derivative (DKN), formed by ring opening of the isoxazole, that is the active HPPD inhibitor. This conversion takes place in the soil, with soil moisture controlling the proportions of IFT and DKN. The soil behaviour of IFT and DKN were described in detail and related to the selectivity of is IFT. For more information on isoxaflutole see Luscombe et al. Proceedings of the Brighton Crop Protection Conference – Weeds 1995, 1, 35-42 and Luscombe and Pallett Pesticide Outlook 1996, 7(6), 29-32.

Mesotrione

Glynn Mitchell of Zeneca described the new maize selective herbicide mesotrione, the second benzoyl cyclohexanodione offering from Zeneca after sulcotrione which has been registered in Europe since 1993. This family of chemicals is chemically related to naturally occurring phytotoxins from Callistemon species. Like isoxaflutole, mesotrione acts by HPPD inhibition. Much detail was given of SAR work done on the dione and benzoyl moieties in the development of mesotrione with the best bioefficacy and crop selectivity.

Pyriftalid

This molecule originated in Dr M Maag and passed with takeovers/mergers to Ciba-Geigy and then Novartis; is is a grasskiller for use in rice. Most of this lecture dealt with the chemical conversion of 7-[(4,6-dimethoxyapyrimidin-2-yl)oxy]phthalide to the S-bridged analogue pyriftalid, which was announced at the 17th Asian Pacific Weed Science Society Conference in Bangkok last year.

Insecticides and fungicides

Spinosyns

Gary Crouse from Dow AgroSciences described this new class of natural product for commercial insect control.
Spinosad (Naturalyte) (a mixture of spinosyn A and spinosyn D) has been launched in several countries for control of chewing insect pests. This lecture centred on the selective modification of the molecule to improve its physical characteristics under field conditions, and the breadth of its pest spectrum. Measurably improved field performance was achieved through improvements in formulation and crystallinity. For more information on spinosyns see the article by Gary Thomson in Pesticide Outlook 1999, 10(2), 78.

Methoxyfenoside
This is the third and newest diacylhydrazine insecticide (a lepidopteran-specific larvicide) to reach the marketplace and was described by Glenn Carlson of Rohm & Haas. Its mode of action is as an insect modifying hormone.

Thiamethoxam
Due to safety, environmental and resistance concerns over such insecticides as organochlorines, organophosphates, carbamates and pyrethroids, there has been interest in such new insecticide classes as the neonicotinoids. Influenced by early work by Shell (nithiazin, 1974) and Bayer (imidacloprid, 1985), Novartis started in this field in 1985, resulting in the discovery of thiamethoxam, as described by Peter M aienisch from N ovartis in Basel. It was first synthesised in 1991 and is now being developed worldwide for use in more than 20 crops. This molecule, announced at the Brighton Conference in 1998, can be prepared very efficiently from S-methyl-N-nitroisothiourea or nitroguinine.

Famoxadone
Jeffrey Sternberg from DuPont Crop Protection Products described the development of this oxazolidinone fungicide which gives excellent control of plant pathogens in the Ascomycete, Basidiomycete and Oomycete classes in grapes, cereals, tomatoes, potatoes and other crops. The development of this molecule started with the procurement of a thiooxo-oxazolidinone from Professor Detlef Geffken at the University of Bonn. After extensive SAR studies and biological testing, over 700 analogues being prepared, famoxadone was advanced to commercial development in the 1990s. The molecule, which was launched at the 9th IUPAC Congress of Pesticide Chemistry in 1999, is a potent inhibitor of mitochondrial electron transport, acting at the same site as the strobilurins, although binding in a different way.

Karate Zeon
This presentation by Ian Shirley from Zeneca Agrochemicals related not to the development of a new molecule but to a new delivery system for the well-known lambda-cyhalothrin insecticide. Microencapsulation technology targets the insecticide to where it is needed and gives comparable biological performance to that of EC formulations, but with an improved acute toxicological profile and a reduction in paraesthesia (subjective facial sensitisation). Dr Shirley
claimed that despite the increased costs of production of the microcapsules, it is an economic technology when one consider. For more information on Karate Zeon see the article by Bob Perrin in Pesticide Outlook 2000, 11(2), 68.

**Indoxacarb**

In the last presentation Stephen McCann from DuPont Crop Protection described the development of indoxacarb – a pyrazoline-based insecticide which acts as a sodium-channel blocker. From an initial pyrazoline lead reported by Phillips-Duphar in 1973, DuPont had put a huge amount of synthetic and biological resources in the 1980s and 1990s towards the development of indoxacarb with a new mode of action which provides high levels of activity against crop pests that are resistant to cholinesterase inhibitors such as carbamates and OPs. Indoxacarb is actually a pro-insecticide, being converted into the active compound by removal of a CO₂Me in the insect gut.

**Conclusion**

Overall the meeting provided useful insights on the latest molecules being developed in the crop protection industry, especially in the search of new modes of action, and safer, more selective compounds. At times one could only wonder at the ingenuity of the chemists involved in these developments. The result was fitting tribute to John Dingwall.

The papers from the meeting will be published in a future special issue of Pest Management Science, also to be dedicated to the memory of John Dingwall.

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**WYE COLLEGE IN MERGER**

Wye College, Kent, UK, merged with Imperial College of Science, Technology and Medicine, London on 1 August 2000; the Wye campus will be known as Imperial College at Wye. Wye College is internationally renowned for research-led teaching in biological sciences, the environment, agricultural economics and business management, agriculture and horticulture with an annual turnover of about £12 million. It was founded by Cardinal John Kempe in 1447 and became a school of the University of London in 1900.

The merger will bring agriculture to Imperial College for the first time and will enable many synergies in environmental, biological and biochemical disciplines. The existing Wye departments (Biological Sciences, Agriculture & Horticulture, Environment and Agricultural Economics & Business Management) will join Imperial’s Department of Biology and the TH Huxley School of Environment, Earth Sciences and Engineering. Nineteen new courses are being offered as a result of the merger. Imperial College at Wye will also continue to offer opportunities for distance-learning and short intensive courses via its award-winning External Programme. Wye agricultural economists have been working with Imperial natural scientists on the economic impacts of pesticide use in developing country agriculture. The merger will offer realistic means of addressing the problems that interrelate agriculture, the environment and sustainable development with those relating to diet and health.