Leslie Crombie

by Donald A. Whiting

1 PERKIN

Leslie Crombie was a leading international figure in natural product chemistry. He achieved his ambitions through natural talent combined with dedicated hard work and great determination, although in his early life he did not have the advantages of full time school and university first degree education. His researches, recorded in over 400 papers, are remarkably varied, with major investigations into the constitution and synthesis of new natural compounds and biosynthesis in higher plants, although his work also included curiosity-driven research on complex condensations and unusual mechanisms. The author had the privilege and pleasure, first of all of carrying out his PhD studies supervised by Leslie, and later of participating in a harmonious research collaboration extending from Leslie's appointment to the Chair of Organic Chemistry at Cardiff until his retirement.

Leslie was born in York, and in the right company would refer to himself as a Yorkshireman. His family moved to Portsmouth in the 1930s, and family circumstances caused Leslie to leave school at 16 to work in the analytical laboratory of a branch of Timothy White and Taylors, a well-known chain of Chemist's shops. When the premises were destroyed by bombing in 1941, Leslie took a new job in the Admiralty's laboratory in Portsmouth Dockyard. In that period he worked on naval matters such as submarine camouflage; submarines on the surface at sea need to be light coloured, to blend in with the horizon, but when off shore need to be dark to merge with the landscape. This problem was solved swabbing the hulls with sodium sulfide in seawater to blacken them when in harbour, reversing the process at sea with hydrogen peroxide. This work formed his first publications in the *Journal of the Royal Naval Scientific Service*. The interest in applied chemistry remained with Leslie throughout his life, and he displayed a remarkable knowledge of topics in materials chemistry and instrumentation, which later he drew on during a long period as the assessor, for the Royal Institute of Chemistry, of the L R I C Applied Subjects.

Leslie Crombie (1923–1999)

During this period Leslie studied chemistry at evening classes at Portsmouth Municipal College and eventually gained an external degree of the University of London with first class Honours in Special Chemistry. With this qualification he was able, in 1946, to embark on PhD research at King's College London, under the supervision of Dr Stanley Harper, then Reader in Organic Chemistry. Harper had worked in Rhodesia on a variety of natural products, particularly on extractives of insecticidal plants, and he gave Leslie the opportunity to work on the pyrethrins, the topic of his thesis (completed in two years) in 1948 and which remained one of his interests throughout his career. Others of Harper's students contemporary with Leslie were his lifelong friends Hugh Reed, who pursued a distinguished career in ICI, and Michael Elliot whose later work at Rothamsted on synthetic pyrethroids proved so significant in agriculture.

Following his PhD, Leslie was appointed to the staff of the Chemistry Department at Imperial College, headed by R. P. Linstead, where he met such notable figures as D. H. R. Barton, B. C. L. Weedon and J. A. Elvidge. Leslie recalled that Barton advised him that, if he wished to get into good problems in natural product chemistry, he should look out for cases in which the isolation of biologically-significant compounds had been achieved by earlier workers, who had not however been able to solve the structures. This advice was to serve him well.

At Imperial College Leslie extended his research interests to insecticidal fatty acid amides, rotenoids and certain synthetic compounds of unknown structure. His publications and growing reputation led to his return to King's in 1958, as Reader, in succession to H. B. Henbest who had been appointed to a chair in Belfast. King's had a very strong group of staff in organic chemistry at the time, led by Professor Donald Hey and including Dr Charles Rees and Dr John Cadogan, as young lecturers. It is interesting to observe that organic chemistry at King's in 1958–59 was carried out with the aid of one IR (recording) and one UV/VIS spectrometer (absorbances at the required wavelengths had to be noted down and plotted by hand). No NMR instrument was available (although one instrument was being home built for kinetic measurements), and Professor Derek Satchell remembers Leslie complaining bitterly at staff meetings that lack of this technique was like having one arm tied behind one's back. There was no MS (molecular masses were determined by osmometry, to an accuracy of around 10%, on a good day). Column chromatography was used (although TLC had been invented, suitable silica was not commercially available, and the technique was little known) as was GLC (although one of Leslie's students had to construct one for his work on hydrogenation of allenes and acetylenes).

Leslie's research continued to make rapid progress at King's and in 1963 he was appointed to the first chair of

DOI: 10.1039/b004067n

organic chemistry at the University of Wales in Cardiff, where he remained until his appointment to the Sir Jesse Boot chair of Organic Chemistry at Nottingham in 1969. A particular characteristic of his tenures was his awareness of the importance of keeping abreast of advances in physical methods and new instrumentation, and using them to tackle hitherto unyielding problems. He constantly and successfully sought funds to upgrade and extend departmental instrumentation to state-of-the-art standards, acquiring for Nottingham new NMR, mass and chiroptical spectrometers, X-ray diffractometers, radiochemical counters and the latest chromatography equipment.

One strand of his work was that of structure determination of natural products, particularly those of agrochemical interest. Among notable examples is the elucidation of the constitutions of the nicandrenoids. These compounds had been isolated from the Peruvian 'Shoo-fly' plant and were reported in *J. Agric. Food Chem*. to have insecticidal properties, being particularly effective against a pest of the tobacco crop. Investigations started at Cardiff revealed a range of novel highly oxygenated plant steroids with a unique ring D aromatic structure. The structural analyses rested on a combination of X-ray crystallographic work for several of the compounds, combined with NMR and chemical correlations for others. Unusually, the X-ray work was carried out within Leslie's group at Nottingham; at the time crystallographic studies were, with very few exceptions, made by specialists remote from the natural product isolation and spectroscopic work. Leslie was one of the earliest organic chemists to see that automatic diffractometers and new computers could allow X-ray analysis to become an integral part of a natural product group. This was in contrast to the view of some established figures, who voiced the opinion that the use of X-rays should be a last resort, since new chemistry, which might have been discovered during traditional chemical degradation, would be lost. He was in fact among the first organic chemists to realise that it was no longer necessary to specialise in just one or two areas of the natural product field.

Leslie's wife Mary, by early education a plant physiologist whom he had first met at the Portsmouth Municipal College, worked with him on a number of productive collaborations. In one of these, his group investigated the extractives from oat roots that are responsible for protection from 'Take-all' disease. This fungal disorder of wheat, barley and rye causes crop losses valued at upwards of £60 million per annum in Britain alone, and an understanding of the compounds concerned in the natural defences of oats may eventually lead to control of the disease. The extractives were non-crystalline and standard NMR spectra gave limited information; the breakthrough came from the measurement of many nuclear Overhauser effects, a rare and early example of the application of this technique to structure determination. It has already proved possible to alter the genes of oats to delete avenacin production and it may be possible to transfer these genes into other cereals. Other notable areas of structural research were those into the insecticidal constituents of the 'mammy tree' (complex coumarins), and the extractives of 'khat', a euphoriant substance widely used in East Africa and a matter of concern to the World Health Organisation.

The pyrethrin insecticides, found in the flower heads of pyrethrum spp. and used in commercial preparations for pest control were an abiding interest. It was typical of the broad sweep of his vision to see quickly the connections between the cyclopropanes chrysanthemic acid (one component of the pyrethrins), presqualene, prephytoene and casbene, and also between the pyrethrin ketols, jasmone and jasmonic acid, an important hormone of plants and fungi. Another longstanding interest was in rotenone, a tropical product once widely used in agriculture but now mainly employed in horticulture as a 'green' insecticide and for clearing waters used in fish farming, before restocking. Extensive work on the biosynthesis of the rotenoids was carried out over many years by Leslie's group resulting in a detailed picture of the processes by which some plants can synthesise these products. This work has facilitated research into transgenic plants that may be able to protect themselves against insect attack. Early interests in fatty acid amides from peppers, reported to be insecticidal, led to much synthetic work in this area, and some recent patents portend the likely development of a commercial product based on his pioneering studies.

Other natural product areas he engaged in included natural chromenes and cannabinoids, the phorbol esters, cordifine, cembrene and casbene, and certain host-specific fungal toxins. However Leslie's scientific curiosity was not confined to natural products, and he also investigated such topics as carbon suboxide (C_3O_2), from maleic and tartaric anhydride derivatives, coloured synthetic products such as Pechmann dyes, xanthophanic and glaucophanic enols, and Feist's compounds, and 'citrylidene malonic acid'. This last, the product of condensation between citral and malonic acid in pyridine, proved to have a tricyclic structure formed by an intramolecular Diels–Alder process. Leslie later noted the parallel between this apparently unique curiosity and certain meroterpenoids, and showed that similar condensations of resorcinols and phloroglucinols with citral and farnesal could open the way to the synthesis of a plethora of natural compounds.

Leslie Crombie's work was honoured by many awards and distinctions. He was elected to a Fellowship of the Royal Society in 1973, and received many RSC awards, including the Pedler, Flintoff, Hugo Muller, Natural Products and Robert Robinson medals of the Royal Society of Chemistry, as well as the American Chemical Society award for Research in Agrochemicals. He was a Fellow of King's College, and received an honorary doctorate by the University of Portsmouth. He gave great service to the Royal Society of Chemistry, the Phytochemical Society of Europe and the European Society of Bio-organic chemistry.

Leslie had a quiet and rather reserved exterior and was always courteous and controlled. He neither sought attention nor liked it very much. Nevertheless he was a determined man, able to play a long patient waiting game in his academic affairs, and resolute in committee. When he became influential in distributing resources, he had no time for what he called 'Buggin's turn' but believed in supporting the best science wherever it was to be found. He was an excellent manager of postgraduates, adept at matching individual talents and characters to suitable problems. His considerable research output might suggest that he was inclined to drive his research students hard. On the contrary he was a model of kindness and support, and gained the respect and affection of generations of postgraduates in whom he instilled respect for the highest standards in science and scientific writing.

Many past students still recall with pleasure the hospitality that Leslie and Mary gave to his research groups. Away from the laboratory he could reveal himself as a man of culture, well read in English and Classical literature, and interested and informed on the arts, education and current affairs. He was above all a totally professional chemist, a fine scholar and a gentleman. The standards he set himself and his students, in research and in publications, are and will remain a model for all generations of scientists.