COVER FEATURE

Professor David J. Robins *

Recipient of the RSC Flintoff medal 1999

Career

David Robins was born in Purley, Surrey, England and attended Purley Grammar School. The enthusiastic and eventful experimentation of one of the Chemistry teachers attracted him towards a career in Chemistry. He obtained his BSc in Chemistry from the University of Exeter in 1966. He stayed on there to carry out research on the biosynthesis of pyrrolizidine alkaloids for his PhD work under the stimulating supervision of David Crout (now Professor at the University of Warwick). He extended this interest in biosynthesis during a two year stay from 1969–1971 at the University of Pittsburgh, USA studying vitamin K biosynthesis with Professor Ronald Bentley. Following brief stays at the Universities of Surrey and Reading, he was appointed a lecturer at the University of Glasgow in 1974. Robins was awarded a DSc by the University of Glasgow in 1987, promoted to Professor of Bioorganic Chemistry in 1990 and elected a Fellow of the Royal Society of Edinburgh in 1994.

Research

Under the stimulating atmosphere provided by 16 other organic chemistry staff at the University of Glasgow, research on the synthesis and biosynthesis of pyrrolizidine alkaloids was very productive and over 180 papers and patents have been published. Pyrrolizidine alkaloids are important natural products because of their widespread occurrence and their hepatotoxicity. The most toxic pyrrolizidine alkaloids contain a 1,2-unsaturated necine diol as part of a macrocyclic dilactone as in dicrotaline **1**. We have studied the synthesis and biosynthesis of these interesting and important alkaloids for many years. The highlights of our synthetic work were that

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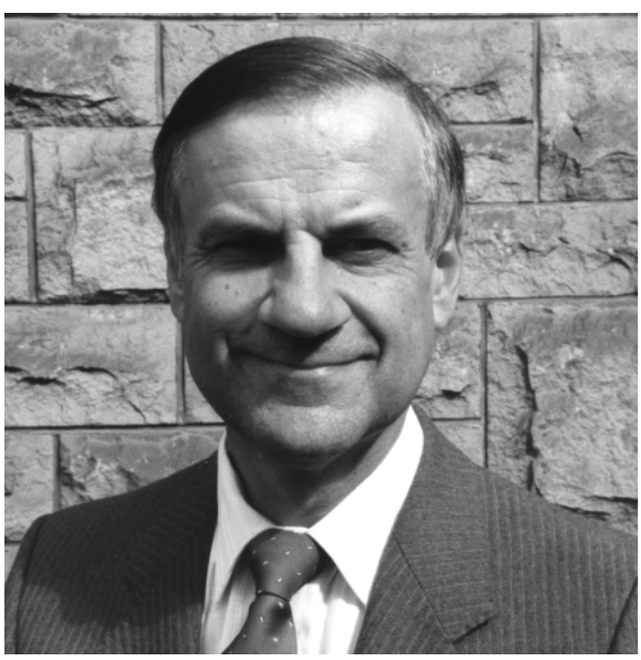
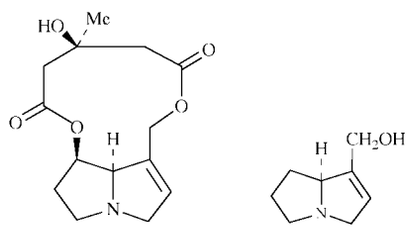
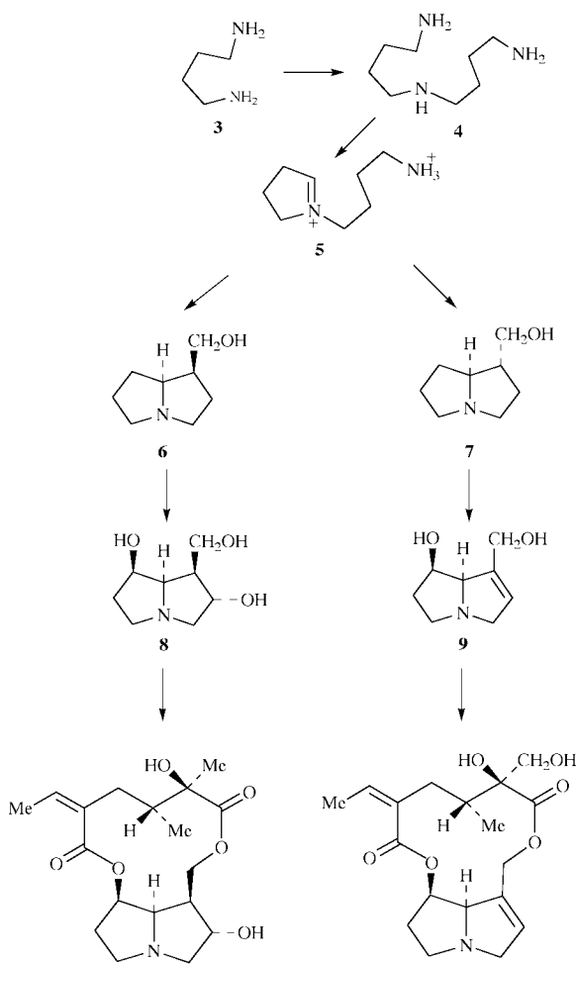




1 **2**

we were able to develop a general method for preparing the hepatotoxic 1,2-unsaturated pyrrolizidine system in our synthesis of (±)-supinidine **2**;[1] the first synthesis of six optically active pyrrolizidine bases (necines) was carried out from 4-hydroxy-L-proline;[2] and we also achieved the first synthesis of a macrocyclic pyrrolizidine alkaloid, dicrotaline **1**.[3]

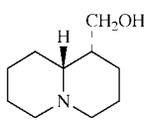
A major part of our work has been the identification of most of the intermediates in the biosynthetic pathway to a variety of necines, particularly rosmarinecine **8** and retronecine **9** shown in Scheme 1.[4] Rosmarinecine is the base portion of rosmarinine



Scheme 1 Biosynthesis of pyrrolizidine alkaloids.

10 which is produced by *Senecio pleistocephalus*, whereas the major alkaloidal constituent of *S. isatideus* is retrorsine **11**. Feeding experiments were carried out with precursors labelled with ^{3}H, ^{13}C, and ^{14}C on these and other plants which produce pyrrolizidine alkaloids. In the biosynthetic pathway, two molecules of putrescine **3** combine to form homospermidine **4**. The action of a transaminase or diamine oxidase generates the iminium ion **5** which undergoes further oxidation, cyclisation in one of two different ways, and reduction to afford the necines **6** and **7**. Two further hydroxylations of **6** lead to rosmarinecine **8** whereas two hydroxylations and a dehydration on **7** yield retronecine.

We extended our studies to quinolizidine alkaloids which are found in *Lupinus* species (*L. polyphyllus* is shown on the cover) using a combination of stable and radioisotopes. Key experiments with precursors labelled with ^{13}C and ^{15}N at adjacent positions demonstrated clearly that retronecine **9** is formed from a precursor (homospermidine **4**) with C_{2v} symmetry,[5] whereas the biosynthesis of lupinine **12** does not involve a symmetrical precursor of this type.[6] We also used ^{13}C–^{15}N labelled cadaverine to show which C–N bonds remain intact in the biosynthesis of a range of tetracyclic quinolizidine alkaloids including sparteine **13** and lupanine **14**.[7]



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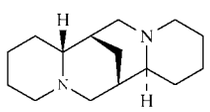

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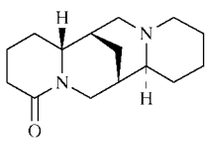

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We established the stereochemistry of many of the enzymic processes involved in the biosynthesis of a number of pyrrolizidine[8] and quinolizidine alkaloids[9] using precursors labelled stereospecifically with deuterium in combination with ^{2}H NMR spectroscopy. For many years with the aid of my wife, Helen, thousands of plants were grown in every available greenhouse and in our garden for the numerous feeding experiments which needed to be carried out during the brief Scottish summers.

Pyrrolizidine alkaloids exert their toxic effects by bifunctional alkylation processes. This encouraged us to design new bifunctional alkylating agents and we are studying their interactions with DNA with Professor John Hartley at University College London Medical School.[10] He showed that one of our new compounds is an 'amazing' alkylating agent. It is 10000 times better at crosslinking DNA than the well-known anticancer drug chlorambucil. The crosslinking of DNA prevents it from unwinding and replicating. Thus cell division is prevented. We are designing and making even more powerful alkylating agents. Many cancer cells are hypoxic (low in oxygen content) and readily reduce suitable oxygenated organic compounds in order to obtain oxygen to go on living. New compounds have been designed by us which are inactive prodrugs in normal cells, but in cancer cells they may be reduced to produce toxic compounds. We shall then attempt to make them more selective by converting them into inactive prodrugs which will only be bioreductively activated to toxic compounds once they get inside cancer cells.

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