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Battersby A R. The biosynthesis of alkaloids. *Proc. Chem. Soc. London* 1963:189-200. [Robert Robinson Laboratories, University of Liverpool, England]

This article pulls together the results of many experiments, carried out on living plants, which were aimed at discovering the chemical pathways by which several key families of alkaloids are constructed. These experiments were among the earliest to depend on the synthesis of radioactively labelled, relatively complex precursors for incorporation studies on the living systems. [The *SCI*® indicates that this paper has been cited in more than 115 publications.]

Probing Nature's Pathways to Alkaloids

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The first stirrings of my thinking about biosynthesis began between 1946 and 1949 when I became involved with the plant alkaloids. I was fascinated by the amazing array of structures they displayed, and I was intensely curious to know how living plants built them. There was no way to tackle these problems then. Only when materials labelled with carbon-14 became available in the late 1940s and early 1950s could a start be made.

Our dream was to explore some striking structural relations between 1-benzylisoquinolines and several other major families of alkaloids, especially to the morphine group first recognized by R. Robinson.[1] In retrospect, it is fortunate that, at the outset, we were not too familiar with the complexities of living systems, because the difficulties foreseen by our biological colleagues were formidable. But on the basis of "nothing ventured, nothing won," we went ahead and injected our synthetic, labelled materials into the plants of interest. We were fortunate that sufficient of the precursors penetrated to the sites of alkaloid synthesis, often with surprisingly large conversions into the final products.[2]

These experiments established the 1-benzylisoquinoline system as the precursor from which not only the morphine alkaloids are biosynthesised but also the protoberberines and the aporphines. What was being observed was nature moulding the available clay by producing a great variety of structures from one type of fundamental starting material.

These studies lasted over many years and benefitted from the invaluable contributions of four senior colleagues, Bob Binks, Jim Staunton, Bob Ramage, and Ted McDonald, and the results we obtained substantiated the original broad structural relations. As our researches developed, they were very much influenced by D.H.R. Barton and T. Cohen's proposals[3] on the role of phenol oxidation.

Perhaps this article has been frequently cited because it was one of the earliest to give sound experimental evidence for the biosynthesis of a variety of natural products—diverse at first sight but demonstrated to be biosynthetically closely related. The article ended by saying "the deepest understanding of alkaloid biosynthesis will come from the combined efforts of chemists, biochemists, and enzymologists." The truth of this can be judged from the progress made by building on the vast body of knowledge of the basic biosynthetic pathways revealed by the labelling experiments to isolate the enzymes of alkaloid biosynthesis.[4] The availability of the enzymes has enabled researchers to fill in blank sections of pathways and to gain knowledge both of the order of events (such as O-methylation and hydroxylation) and of some of the mechanistic details of the enzymic transformations. Progress along these lines is bound to accelerate. But the methodology, techniques, and experience from the original researches on alkaloids using labelled precursors were the springboard for another major development. They allowed the Cambridge group to start studying the biosynthesis of the pigments of life, such as heme and vitamin B_{12}, in 1968 and so to break much new ground.[5,6]

1. **Robinson R.** *The structural relations of natural products.* Oxford, England: Clarenden Press, 1955. (Cited 260 times.)
2. **Battersby A R, Herbert R B, McDonald E, Ramage R & Clements J H.** Biosynthesis of colchicine from the 1-phenethylisoquinoline system. *J. Chem. Soc. Perkin Trans,* 1972:1741-6.
3. **Barton D H R & Cohen T.** Some biogenetic aspects of phenol oxidation. *Festschrift A. Stoll.* Basel. Switzerland: Birkhauser, 1957. p. 117-43. (Cited 310 times.)
4. **Rueffer M & Zenk M H.** S-adenosyl-L-methionine: (S)-7,8,13,14-tetrahydroberberine-cis-N-methyltransferase, a branch point enzyme in the biosynthesis of benzophenanthridine and protopine alkaloids. *Tetrahedron Lett.* 27:5603-4, 1986.
5. **Battersby A R.** Biosynthesis of vitamin B_{12}. *Account. Chem. Res.* 19:147, 1986.
6. **Battersby A R & Leeper F J.** Biosynthesis of the pigments of life: mechanistic studies on the conversion of porphobilinogen to uroporphyrinogen Ill. *Chem. Rev.* 90:1261-74, 1990.

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