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Biosynthesis of the Piperidine Alkaloids. The C_6–C_2 Units of Sedamine and Lobinaline

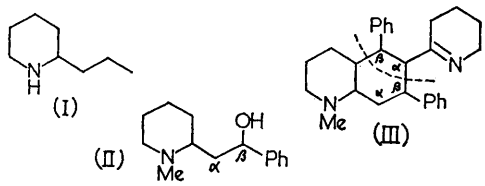
By R. N. Gupta and I. D. Spenser

(*Department of Chemistry, McMaster University, Hamilton, Ontario, Canada*)

The close structural relationship between the alkaloids of hemlock [*e.g.*, coniine (I)] and those of *Sedum* [*e.g.*, sedamine (II)] and of *Lobelia* [*e.g.*, 8-phenyl-lobelol[1] (II)] appears to indicate analogy of biogenetic origin.[2] The carbon skeleton of coniine (I) has been shown by Leete[3] to be derived in its entirety from four acetyl units in linear head-to-tail array. By analogy sedamine (II) should be generated from a polyacyl chain formed by combination of three acetyl units with a benzoyl moiety,[2] and lobinaline[4,5] (III), which can be regarded as a modified dimer of (II), should arise from two such chains.

The evidence we now offer is incompatible with such a polyacyl origin of sedamine or of lobinaline. Our results demonstrate that the C_6–C_2 side-chain of sedamine is derived as an intact unit from phenylalanine, and indicate a similar origin of the corresponding fragments of lobinaline.

Plants of *Sedum acre* L., which had been exposed to [2-^{14}C]- and [3-^{14}C]-phenylalanine in separate feeding experiments, yielded active sedamine, which was degraded to locate the sites of labelling. Distillation with zinc dust[6] released the side-chain in the form of acetophenone, which was isolated as the semicarbazone and oxidized further to benzoic acid. Oxidation[1] of sedamine gave *N*-methylpipecolic acid and benzoic acid which was then converted into aniline. All activity of the sedamine from [2-^{14}C]phenylalanine was confined to the α-position of the side-chain (II), all activity of the sedamine from the [3-^{14}C]radiomer to the β-position.



In a third experiment a mixture of [2-^{14}C]- and [3-^{14}C]-phenylalanine of known isotope distribution was administered to *Sedium acre*. The sedamine obtained from these plants showed a distribution of label (α, 45 ± 1; β, 55 ± 1%) corresponding to that of the doubly labelled precursor (2-^{14}C, 46 ± 1; 3-^{14}C, 54 ± 1%). The C_6—C_2 side-chain of sedamine is therefore derived as a unit from phenylalanine.

Radioactive lobinaline was isolated from plants of *Lobelia cardinalis* L., to which [2-^{14}C]-, [3-^{14}C]-, and [2,3-^{14}C]-phenylalanine had been administered, and was purified as the acetyl derivative.[4] The compound proved to be remarkably resistant to controlled degradation (*cf.* ref. 4.). The only useful product which was obtainable was *p*-nitrobenzoic acid, arising on oxidation of acetyllobinaline with nitric acid followed by alkaline

permanganate. *p*-Nitrobenzoic acid, obtained from the lobinaline derived from [3-^{14}C]phenylalanine, was labelled solely in the carboxyl group and its specific activity was half that of the alkaloid. Since lobinaline contains two *C*-phenyl moieties specific derivation of at least one of these C_6–C_1 units from phenylalanine is thereby demonstrated. [*Carboxy*-^{14}C]Benzoic acid, however, was not incorporated into lobinaline.

Lobinaline derived from [2,3-^{14}C]phenylalanine yielded *p*-nitrobenzoic acid whose specific activity relative to that of the intact alkaloid was consistent with and thus indicative of the incorporation of at least one intact C_6–C_2 unit derived from phenylalanine.

Activity from [6-^{14}C]lysine enters both alkaloids. Even though degradation is as yet incomplete it appears that lysine is the precursor of the piperidine ring of sedamine and of the hetero-rings of lobinaline. Active sedamine derived from lysine gave inactive acetophenone. Hofmann degradation of lysine-derived lobinaline, followed by ozonolysis, gave formaldehyde, isolated as the dimethone, whose specific activity was one quarter of that of the intact alkaloid. Benzoic acid, obtained by permanganate oxidation of the Hofmann product, was inactive.

These results demonstrate that the biosynthetic origin of sedamine and of lobinaline differs fundamentally from that of coniine. They show that structural relations can be biogenetically misleading and serve as an object lesson of the danger of argument by analogy, where biosynthetic pathways are concerned.

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