Biosynthesis of the Piperidine Alkaloids: Origin of the Piperidine Nucleus of *N*-Methylisopelletierine

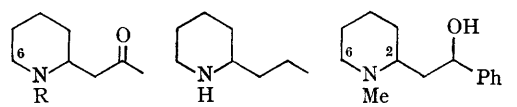
By R. N. GUPTA and IAN D. SPENSER*

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

ISOPELLETIERINE (I) and its *N*-methyl derivative (II) have been isolated from a number of plant genera, including *Sedum*.[1] Their carbon skeleton is identical with that of the hemlock alkaloids [*e.g.*, coniine (III)]. The hemlock alkaloids are of polyketide origin.[2] The biosynthetic derivation of isopelletierine has not been established. However, a Sedum alkaloid of related structure, sedamine (IV), has been shown to originate from amino-acids and not from a polyacyl precursor.[3,4] Its piperidine nucleus is derived from lysine. Activity from [2-^{14}C]lysine was confined to C-2, activity from [6-^{14}C]lysine to C-6 of the nucleus of sedamine.[4]

We now present evidence which demonstrates that the piperidine ring of *N*-methylisopelletierine (II), unlike that of coniine (III), is derived from lysine.

Radioactive *N*-methylisopelletierine was isolated, after addition of carrier, from excised shoots of *Sedum sarmentosum*,[5] which had been kept in contact with [6-^{14}C]lysine for 48 hr. Degradation of the labelled product yielded C-6 of the piperidine nucleus as formaldehyde, isolated as the dimedone derivative, whose specific activity was identical, within experimental error, with that of the intact alkaloid. All activity from [6-^{14}C]-lysine was thus confined to C-6 of the nucleus of *N*-methylisopelletierine (II).



(I) R=H
(II) R=Me

(III)

(IV)

In a further experiment, doubly labelled [6-^{14}C,4,5-$^{3}H_2$]lysine was administered to *S. sarmentosum* shoots. The *N*-methylisopelletierine which was isolated showed a ^{14}C/^{3}H ratio identical with that of the administered doubly labelled lysine. Similarly, in *S. acre*, doubly labelled [6-^{14}C,4,5-$^{3}H_2$]-lysine was incorporated into sedamine (IV) without change of the ^{14}C/^{3}H ratio.

These results show that the piperidine nucleus of *N*-methylisopelletierine, like that of sedamine[3,4]

and of anabasine,[6,7] but unlike that of the hemlock bases,[2] originates from lysine, by way of a non-symmetrical intermediate. Since the $^{14}C/^{3}H$ ratio was maintained in the products obtained when $^{14}C,^{3}H$-labelled lysine served as the precursor of *N*-methylisopelletierine and of sedamine, the non-symmetrical intermediate is more likely to be α-keto-ε-aminohexanoic acid than α-aminoadipic δ-semialdehyde (*cf.* ref. 7). If free α-aminoadipic δ-semialdehyde were an intermediate, incorporation of [5-^{3}H]lysine into the piperidine nucleus would be expected to be accompanied by loss of tritium.

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