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BIOSYNTHESIS OF PIPERIDINE ALKALOIDS

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Robinson's hypothesis (1) that lysine or its biological equivalent is the precursor of the piperidine ring in naturally occurring piperidine derivatives has been borne out by many tracer experiments. Isotopically labelled lysine has been shown to be incorporated into the piperidine ring of anabasine (2), into the hydroxy pipecolic acids in plants (3) and into pipecolic acid in animal tissues (4), microorganisms (5) and in plants (6). Recently Leete (7) has demonstrated quite a different biosynthetic pathway for coniine I in hemlock from four acetate units and without involvement of lysine. More recently Gupta and Spenser (8) have shown that sedamine II and lobinaline III, though structurally related to coniine are derived from lysine and phenyl alanine in agreement with Robinson's hypothesis. It is necessary to determine which of these pathways to the piperidine alkaloids is the major one.

Because of its close relationship to the hemlock alkaloids one of the alkaloids chosen for investigation was N-methyl isopelletierine. It may be considered to be an intermediate in the biosynthesis of the hemlock alkaloid, N-methylconiine from either acetate alone or from acetate and lysine. Our results demonstrate that the C_3 side chain of N-methylisopelletierine is derived from acetate and acetate is shown not to be involved in the biosynthesis of the hetero-ring.

A three year old Punica granatum nana plant, fed by a conventional wick arrangement with 1-^{14}C-acetate (total activity 2.2 x 10^8 counts/min.) yielded radioactive N-methyl isopelletierine (specific activity 8.9 x 10^4 counts/min./mmole; percentage incorporation 0.024). The active alkaloid was degraded to determine the location of radioactivity by the following method. 2'-phenyl-N-methylsedridine obtained by the action of phenyllithium on N-methylisopelletierine was oxidised with alkaline permanganate to yield benzoic acid (specific activity 8.2 x 10^4 counts/min./mmole). Over 90% of the activity of the N-methylisopelletierine was thus shown to be located at the 2' position on the side chain.

In another experiment 2-^{14}C-lysine (total activity 0.1m.c.)was fed

to a second P. granatum nana plant. Radioactive N-methyl isopelletierine (percentage incorporation 0.01) was again isolated. Although the degradation of the active alkaloid is as yet incomplete it would appear that lysine is the precursor of the piperidine ring. Chromic acid oxidation of the active N-methyl isopelletierine gave N-methyl pipecolic acid and inactive acetic acid. It would appear unlikely from this result that lysine was being degraded initially to acetic acid which was then being utilised for the synthesis of N-methyl isopelletierine (6).

Administration of 2-^{14}C lysine to Withania somnifera plants yielded active anaferine V (percentage incorporation 0.01). Administration of 2-^{14}C-lysine to Lobelia syphilitica plants yielded active lobeline (percentage incorporation 0.011) while in a separate experiment 1-^{14}C acetate fed to the same plants yielded inactive lobeline VI. These alkaloids have not as yet been degraded to show the location of radioactivity.

Our results to date appear to substantiate the role of lysine in the biosynthesis of the hetero ring of the piperidine alkaloids.

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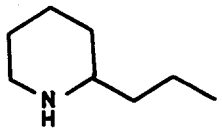

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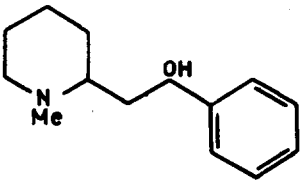

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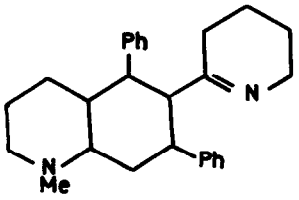

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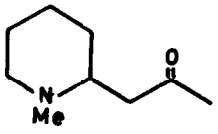

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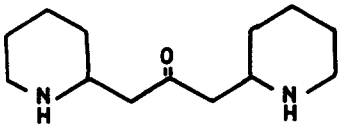

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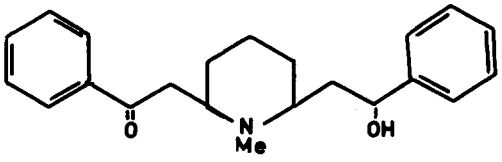

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