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BIOSYNTHESIS OF THE VINCA ALKALOIDS. THE INCORPORATION OF GERANIOL-3-^{14}C INTO CATHARANTHINE AND VINDOLINE

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Recently Battersby (1), Arigoni (2), Scott (3), and their research teams independently discovered that geraniol is a precursor of the non-tryptophan derived portion of the indole alkaloids found in *Vinca rosea* . The pattern of labelling found in ajmalicine, catharanthine, and vindoline derived from geraniol-2-^{14}C was consistent with the intermediate formation of a cyclopentanoid monoterpene which then underwent bond cleavages and rearrangement as suggested five years ago by Thomas (4) and Wenkert (5). Preliminary reports (6-9) on the incorporation of labelled mevalonic acid into ajmalicine, catharanthine, 1,2-dehydroaspidospermidine, reserpinine, serpentine, and vindoline, led us also to consider geraniol a logical precursor of these alkaloids.

Geraniol-3-^{14}C was prepared by the route illustrated in Fig. 1. 5-Bromo-2-methyl-2-pentene (I) (10) was converted to its Grignard derivative and carboxylated with carbon dioxide-^{14}C yielding 5-methyl-4-hexenoic acid-1-^{14}C (II).

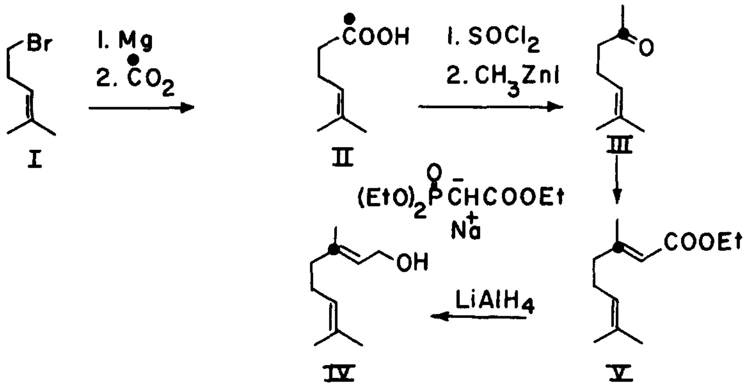

Figure 1. Synthesis of Geraniol-3-^{14}C

This acid was converted to its acid chloride and reacted with methylzinc iodide in ether yielding 6-methyl-5-heptene-2-one-2-^{14}C (III) . This ketone was condensed with the sodium salt of triethylphosphonacetate yielding the ester V, which on reduction with lithium aluminum hydride afforded geraniol-3-^{14}C (IV). The geraniol-3-^{14}C (17.6 mg., 75µc.) was emulsified in water with 0.05 ml. of Tween 80,and excised shoots of Vinca rosea plants placed in this solution. The shoots were harvested after four days when they had absorbed 95 % of the radioactivity from the solution . Radioactive catharanthine (6.84×10^5 d.p.m./mM.) and vindoline (5.69×10^5 d.p.m./mM.) were isolated from the plants . The monoterpene hypothesis requires that catharanthine (VI) and vindoline (VII) derived from geraniol-3-^{14}C should be labelled at C-20 as illustrated in Figure 2. Degradations indicated that this was so . A Kuhn-Roth oxidation of catharanthine yielded acetic and propionic acids having the same specific activity as the

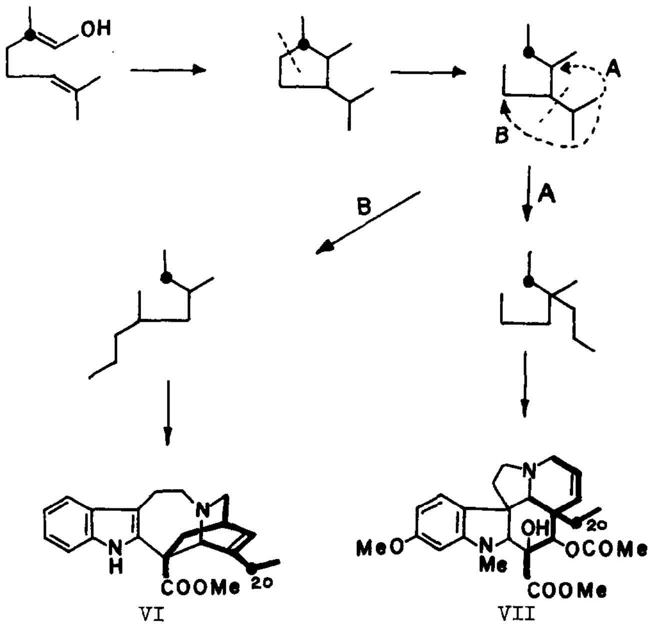

Figure 2. The incorporation of C-10 units into catharanthine and vindoline

catharanthine . A Schmidt reaction on the acetic acid yielded carbon dioxide (95 % of the total activity) and inactive methylamine . The vindoline was hydrolysed yielding acetic acid (inactive) and desacetylvindoline which was subjected to a Kuhn-Roth oxidation yielding acetic and propionic acids having the same specific activity as the vindoline . A Schmidt reaction on the acetic acid yielded carbon dioxide (99 % of the total activity) and inactive methylamine. Our results thus complement those of Battersby, Arigoni, and Scott, and confirm the monoterpene hypothesis.

Acknowledgement

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