

Biosynthesis of the Indole Alkaloids: Vindoline

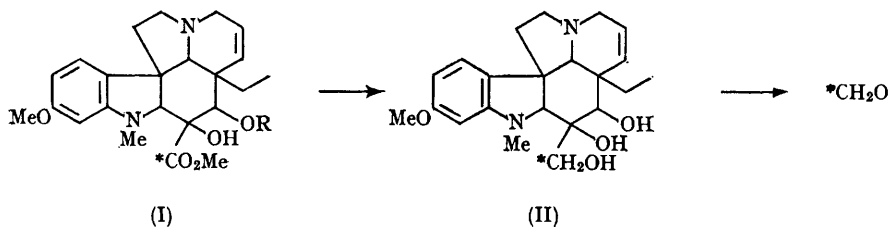
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IN marked contrast to previous experiments designed to test the incorporation of labelled tyrosine,¹ alanine,¹ mevalonate,¹ and acetate^{1,2} into the non-tryptophan-derived segment of ajmaline in *Rauwolfia serpentina* we recently showed³ that

gave a product with constant radioactivity (0.62×10^5 c./m./mmole). The methoxycarbonyl carbon (C*) thus contains 22.0% of the total radioactivity of vindoline, in good agreement with the second of the predicted values of 0, 25, or 50%.

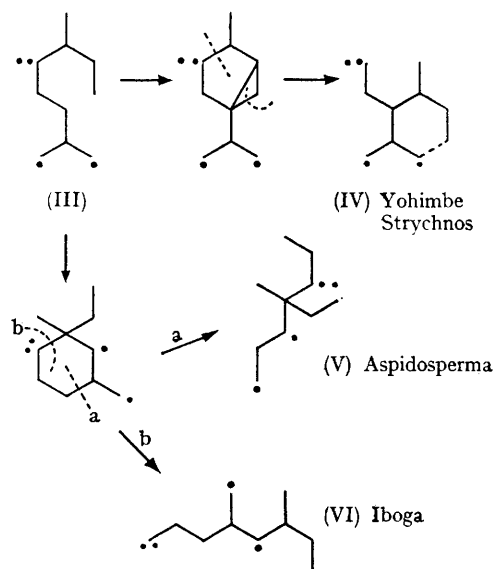


[2-¹⁴C] mevalonic acid lactone served as a precursor for the aspidosperma-type alkaloid vindoline (I, R = Ac) in *Catharanthus roseus* G. Don). We now present experimental evidence which supports the view³⁻⁵ that all of the major indole alkaloids of the *Rauwolfia*, *Yohimbé*, *Strychnos*, and *Cinchona* families are to be regarded as a new class of monoterpenoids.

Hydroponic administration of [2-¹⁴C]DL-mevalonic acid lactone (0.30 mc.) to freshly cut shoots of *C. roseus*, and isolation⁶ after seven days gave vindoline hydrochloride of constant radioactivity (0.5% incorporation; 2.79×10^5 c./m./mmole). Hydrolysis to desacetylvindoline⁶ (I, R = H) (2.78×10^5 c./m./mmole) showed that no radioactivity had been introduced by degradation of mevalonate into the acetate function of vindoline. Lithium aluminium hydride reduction of (I, R = H or Ac) gave vindolinol⁶ (II) retaining the same specific activity (no incorporation in ester *methyl*).

The radioactive vindolinol was treated with two molar equivalents of periodic acid in aqueous ethanol and the liberated formaldehyde isolated as the crystalline dimedone derivative.⁷ Rigorous purification by chromatography and crystallisation

The finding that one quarter of the radioactivity is at C* accords with mevalonoid derivation of



¹ E. Leete, S. Ghosal, and P. N. Edwards, *J. Amer. Chem. Soc.*, 1962, **84**, 1068; E. Leete and S. Ghosal, *Tetrahedron Letters*, 1962, 1179.

² A. R. Battersby, R. Binks, W. Lawrie, G. V. Parry, and B. R. Webster, *Proc. Chem. Soc.*, 1963, 369.

³ T. Money, I. G. Wright, F. McCapra, and A. I. Scott, *Proc. Nat. Acad. Sci. U.S.A.*, 1965, **53**, 901.

⁴ E. Wenkert, *J. Amer. Chem. Soc.*, 1962, **84**, 98.

⁵ R. Thomas, *Tetrahedron Letters*, 1961, 544.

⁶ M. Gorman, N. Neuss, G. Svoboda, A. J. Barnes, Jr., and N. J. Cone, *J. Amer. Pharm. Assoc. (Sci. Edn.)*, 1959, **48**, 256.

⁷ J. F. Walker, "Formaldehyde," Reinhold, New York, 1953.

the monoterpenoid plumiericin⁸ where equipartition of the terminal methyl label (as in II) also occurred.

Further degradation to locate the remaining labelled carbon atoms is in progress and comment on the detailed mode of assembly of the C₁₀-portion must await these experiments. Meanwhile, the terpenoid pathway to the three main classes of indole alkaloid may be represented conveniently by (III) → (IV), (V), and (VI). Recent observations

on formate/acetate incorporation^{2,9,10} together with the present results render the "branched acetate-malonate" derivation¹ untenable.

Essentially identical, independent results have emerged from the work of Professor D. Arigoni employing *C. roseus*, but using a different scheme of degradation, as described in the accompanying Communication.

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⁸ D. A. Yeowell and H. Schmid, *Experientia*, 1964, **20**, 250.

⁹ H. Goeggel and D. Arigoni, *Experientia*, 1965, **21**, 369.

¹⁰ D. H. R. Barton, G. W. Kirby, R. H. Prager, and E. M. Wilson, *J. Chem. Soc.*, 1965, 3990.