The Mevalonoid Nature of Vindoline and Reserpinine

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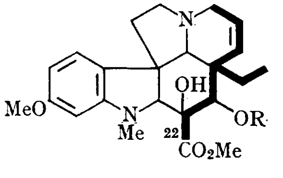
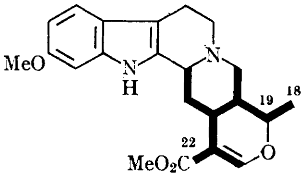
MANY different theories have been put forward in order to account for the origin of the non-tryptophan-derived C_9—C_{10} moieties of various indole alkaloids[1] [*cf. e.g.* the thickened bonds in (I) and (II)]. So far, none has been unequivocally supported by adequate feeding experiments. In particular, the repeated claim[2] that formation of such fragments involves participation of one formate, one malonate, and three acetate units has not been substantiated by other workers.[3] We now provide evidence for the mevalonoid origin of two such alkaloids.

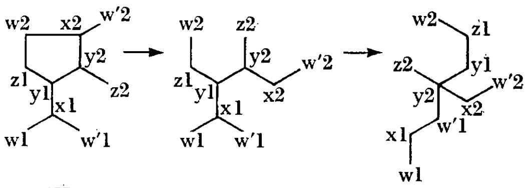


(I)



(II)

Feeding of sodium DL-[2-^{14}C]mevalonate to 1—2 months old shoots of *Vinca rosea* L. (syn. *Catharantus roseus* G. Don) provided *inter alia* radioactive vindoline (I, R = Ac)[4] (0·12% incorporation). A similar incorporation has recently been reported by T. Money *et al.*[5] Hydrolysis of (I, R = Ac) led to the *O*-desacetyl derivative (I, R = H)[6] containing all (99%) the radioactivity of the starting material. The *O*- and *N*-methyl groups isolated by Zeisel determination as well as the propionic acid resulting from the ethyl side chain on Kuhn–Roth oxidation proved to be free of radioactivity. Upon pyrolysis[4] of the hydrochloride of (I, R = Ac), C-22 was isolated as CO_2



(III) (IV) (V)

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[1] For a general review *cf.* E. Leete in P. Bernfeld, "Biogenesis of Natural Compounds," Pergamon Press, 1963, p. 768; A. R. Battersby, "Biogenesi delle Sostanze Naturali," Accademia Nazionale dei Lincei, Roma, 1964, p. 47.

[2] (a), P. N. Edwards and E. Leete, *Chem. and Ind.*, 1961, **1666**; (b), E. Leete and S. Ghosal, *Tetrahedron Letters*, 1962, 1179; (c), E. Leete, S. Ghosal, and P. N. Edwards, *J. Amer. Chem. Soc.*, 1962, **84**, 1068; *cf.* also K. Mothes, D. Gröger, and K. Stolle, *Tetrahedron Letters*, 1964, 2579.

[3] (a), A. R. Battersby, R. Binks, W. Lawrie, G. V. Parry, and B. R. Webster, *Proc. Chem. Soc.*, 1963, **369**; (b), H. Goeggel and D. Arigoni, *Experientia*, 1965, **21**, 369; (c), D. H. R. Barton, G. W. Kirby, R. H. Prager, and E. M. Wilson, *J. Chem. Soc.*, 1965, **3990**.

[4] M. Gorman, N. Neuss, and K. Biemann, *J. Amer. Chem. Soc.*, 1962, **84**, 1058.

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

[6] M. Gorman, N. Neuss, G. H. Svoboda, A. J. Barnes, jun., and N. J. Cone, *J. Amer. Pharm. Assoc., Sci. Edn.*, 1959, **48**, 256.

and shown to contain 22·5% of the total radioactivity.

Similarly, radioactive reserpine (II)[7] was isolated from *Vinca major* L. shoots, to which sodium DL-[2-^{14}C]mevalonate had been administered (0·01% incorporation). According to degradations carried out as detailed in a previous paper,[3b] 26% of the activity was confined to C-22; C-18 carried less than 3% of the label and C-19 proved to be unlabelled. In this case, however, an appreciable scatter of the label into the C_1-pool of the plant is indicated by the presence of *ca.* 7% of the activity in each of the two *O*-methyl groups of (II). These are known[3b] to be derived from the *S*-methyl group of L-methionine.

Our results are consistent with the biogenetic scheme[1] involving the intermediacy of monoterpenes, as in (III), from which the required fragments (IV) and (V) can formally be derived as indicated by use of Klyne's notation.[8] In addition, the observed values require in both cases equilibration of the w1 and w'1 carbon atoms in one of the precursors. Recent work on the biosynthesis of the monoterpenoid plumiericin[9] provides a welcome precedent for such a situation.

Analogous results on the biosynthesis of vindoline are reported in the accompanying paper by A. I Scott and co-workers.

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[7] (a), E. Schlittler, H. Saner, and J. M. Müller, *Experientia*, 1954, **10**, 133; (b), A. Hofmann, *Helv. Chim. Acta*, 1954, **37**, 849.

[8] W. Klyne, *Chem. and Ind.*, 1954, 725.

[9] D. A. Yeowell and H. Schmid, *Experientia*, 1964, **20**, 250.