Biosynthesis of the Indole Alkaloids from a Monoterpene

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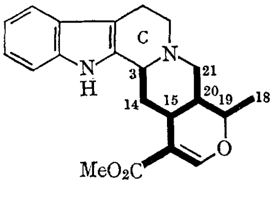
IT has recently been shown that the C_{9-10} unit of the indole alkaloids [thickened bonds in (I), (III), and (IV)] is of mevalonoid origin. Degradative evidence was presented for vindoline and reserpinine,[1] for vindoline,[2] and for catharanthine, ajmalicine, and 1,2-dehydroaspidospermidine,[3] these representing the three major groups of alkaloids. Importantly, the labelling pattern established[3] for catharanthine and dehydroaspidospermidine derived from sodium [2-^{14}C]-, and [3-^{14}C]-mevalonate (a) supported the theory[4] that the C_{9-10} unit is related to the cyclopentanoid monoterpene skeleton (VI) rather than the alternative proposal[2] and (b) was in agreement with head-to-tail combination of the two C_5-units which, on current knowledge of isoprenoid biosynthesis,[5] should lead to geraniol as the C_{10}-precursor. We now report that geraniol is a precursor of representative examples of the *Corynanthe*, *Iboga*, and *Aspidosperma* groups of bases which together account for the majority of indole alkaloids.

[2-^{14}C]Geraniol (V) was synthesised from 6-methylhept-5-en-2-one and methyl [2-^{14}C]-bromoacetate by the standard route. The product was converted largely into the corresponding pyrophosphate[6] and the mixed phosphate esters were fed in aqueous solution as the sodium salts to *Vinca rosea* plants. After two weeks, the following alkaloids and incorporations were obtained: ajmalicine (I, 0·16%), serpentine (I, ring-c aromatised, 0·6%), catharanthine (III, 0·2%) and vindoline (IV, R = Ac, 0·2%). These incorporations are appreciably higher than had been obtained from sodium mevalonate under the same conditions.

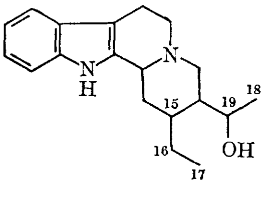
Ajmalicine (I) was converted,[7] with elimination of the methoxycarbonyl group, into ajmaliciol (II, 100% of total activity); it follows that the CO_2Me group carries no radioactivity. The acetic acid (from C-16 and -17 and C-18 and -19) and the propionic acid (from C-15, -16, and -17) isolated by Kuhn–Roth oxidation were both totally radioinactive. This limits the labelling of ajmalicine (I) to four sites (C-3, -14, -20, and -21), the expected position being C-20.

Kuhn–Roth oxidation of catharanthine (III) gave radio-inactive acetic acid together with propionic acid (101% of total activity). Similar oxidation of desacetylvindoline (IV, R = H) again yielded inactive acetic acid and active propionic acid (98% of total activity). Thus, C-4 of catharanthine (III) and C-5 of vindoline (IV, R = Ac) carry essentially all the activity of these alkaloids.

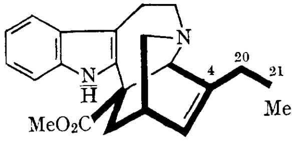
These results establish the specific incorporation of geraniol into the three types of alkaloid in a way entirely consistent with the annexed scheme. Structures (VII), (VIII), and (IX) represent the C_{10} units of the *Corynanthe*, *Iboga*, and *Aspidosperma* families without indication of the state of oxidation.



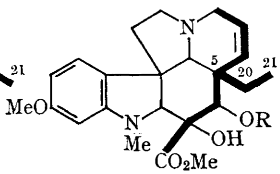
(I)



(II)

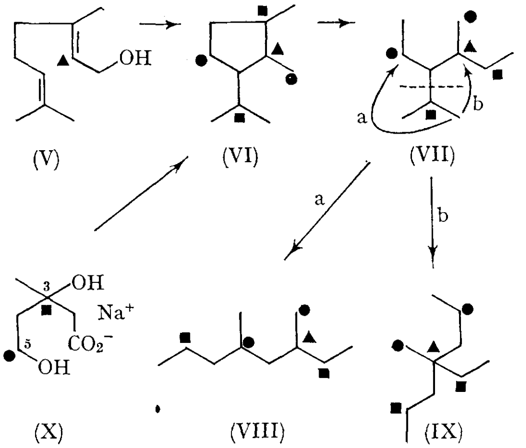


(III)



(IV)

Further evidence was obtained (a) by degradation of serpentine (I, ring-c aromatised) isolated from *V. rosea* plants fed with sodium [3-^{14}C]-mevalonate (see X); the results from Kuhn–Roth and Schmidt reactions proved C-19 to carry 42% of the total activity in agreement with our earlier work on the *Aspidosperma* skeleton[3] (b) by Kuhn–Roth degradation of catharanthine (III) and desacetylvindoline (IV, R = H) derived from sodium [5-^{14}C]mevalonate each of which afforded radio-inactive propionic acid originating, respectively, from C-4, -20, -21, and C-5, -20, -21. These results provide further strong support for the sequence (X) → (V) → (VI) → (VII) → (VIII) and (IX). Experiments are in hand with 4- and 6-labelled mevalonic acid and with multiply-labelled geraniols to elucidate the detailed pathway from geraniol to the alkaloids.



Analogous degradative results for vindoline derived from [2-^{14}C]geraniol are reported in the accompanying Communications from Arigoni and Scott and their co-workers.

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