Biosynthesis of the Indole Alkaloids

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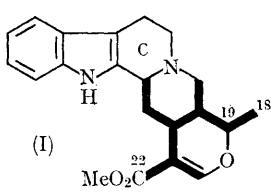
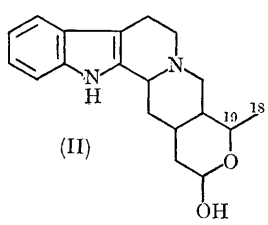
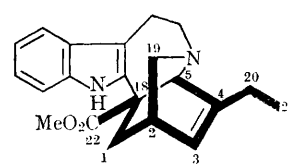
OUR previous researches[1,2] eliminated two of the four biogenetic schemes[3] which had been proposed to account for the origin of the C_{9-10} unit of the indole and Ipecacuanha alkaloids [thickened bonds in (I), (III), and (V)]. A third scheme, based upon a one-carbon unit, acetic and malonic acids, had received experimental support[4] but this too has been firmly excluded.[1,2,5-7] Importantly, the proof that a one-carbon unit is *not* involved in the biosynthesis[1,2,5,6] directed attention to the fourth theory[8] which suggested a relationship of the C_{9-10} unit to the cyclopentanoid monoterpene skeleton (VIII). Pointers in favour of this idea came from the incorporation of labelled mevalonic acid into various indole[9,5,2] and Ipecacuanha[2] alkaloids. We now report degradative results[10] which show the mevalonoid origin of representative



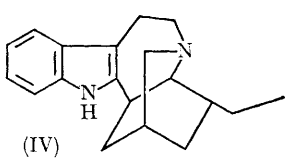
(I)



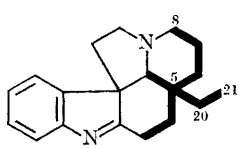
(II)



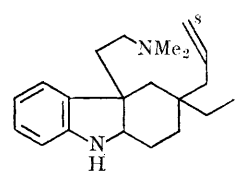
(III)



(IV)



(V)



(VI)

(I) to yield (II) and from dihydrocatharanthine to give epi-ibogamine[12] (IV) showed by the changes in molar activities that C-22 of (I) and (III) carry, respectively, 24% and 23% of the original total activity. These results establish the specific incorporation of mevalonic acid into the alkaloids (I) and (III) in a way consistent with the annexed scheme.[8] In this, C-2 and C-6 of one mevalonate unit have been rendered equivalent as observed for plumeride[13] (see also below). Kuhn–Roth oxidation of (III) gave inactive propionic acid and dehydrogenation of (III) over palladium[12] yielded 3-ethylpyridine (48% of total activity). A partial assignment of the radioactivity in (III) can thus be made: C-22, 23%; C-1 + C-18 by difference, 29%; and 48% located at some point(s) in C-2,-3,-5 and -19. These results are entirely consistent with the examples from the three major classes of indole alkaloids and give insight into the mode of linkage of the two C_5 units.

Sodium (±)-[2-^{14}C]mevalonate (VII) was incorporated by *Vinca rosea* plants to yield radioactive vindoline (0·05% incorporation), ajmalicine (I; 0·003% incorporation), catharanthine (III; 0·04% incorporation) and serpentine (I; ring-c aromatised; 0·02% incorporation). The *O*-methyl groups of (I) and (III) were shown to carry no significant radioactivity by Zeisel determination. Both alkaloids were further proved to be radiochemically pure by dilution and by conversion into a suitable derivative of unchanged molar activity. Elimination of the methoxycarbonyl group[11] from scheme shown (requires C-22, 25%; C-1, 25%; C-19, 50%).

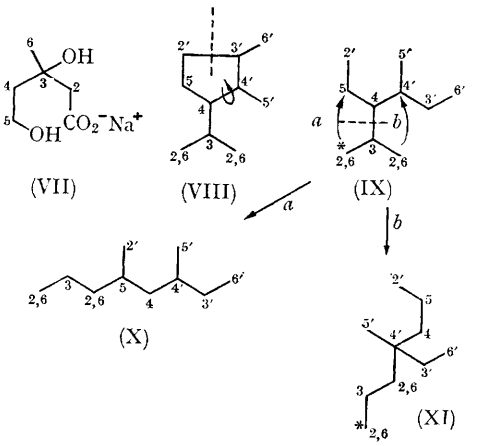
Rhazia stricta plants similarly incorporated sodium (±)-[2-^{14}C]mevalonate to afford radioactive 1,2-dehydroaspidospermidine[14] (V, 0·15% incorporation) which was reduced to aspidospermidine.[14] Kuhn–Roth oxidation established that C-5, -20, and -21 carried no radioactivity. Further degradation by Emde and Hofmann steps[15] to the base (VI) allowed the isolation of C-8 as formaldehyde (65 ± 6% of total). Since the starred carbon in (XI) is lost during the formation of (V), the expected value for C-8 (of V) is 67% of the total activity in the complete absence of scatter. The same alkaloid isolated from plants

fed with sodium (±)-[3-^{14}C]mevalonate (0·15% incorporation) was similarly reduced and the product oxidised (Kuhn–Roth) to acetic acid (47% of total activity) and propionic acid (47% of total). Schmidt degradation of the acetic acid gave inactive methylamine. It follows that C-20 of (V) carries 47% of the original activity whilst C-5 and -21 are essentially radio-inactive.

Independent studies by Arigoni and Scott and their respective co-workers have been in progress concurrently. They showed that vindoline[16,17] and reserpinine[17] derived from [2-^{14}C]mevalonic acid carry, respectively, 22% and 26% of the total activity at the positions corresponding to the starred carbon atom in (IX) and (XI). There is thus exact agreement between their findings and the corresponding portion of the work outlined above.

All our results are in keeping with the illustrated scheme and they eliminate the recent alternative proposal[16] which requires labelling patterns for (III) and (V) differing from those found.

Experiments with 4-, 5-, and 6-labelled mevalonic acid are in progress to gain further knowledge of the biosynthesis.



(*Received, December 1st*, 1965; *Com.* 752.)

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