Further Studies on Rearrangements during Biosynthesis of Indole Alkaloids

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Summary [5-^{3}H]Loganin (**1**) is incorporated into (**7**), (**10**), and (**12**) to label C-3 in each case, so supporting current views of the biosynthetic stages beyond loganin.

[5-^{3}H,O-*methyl*-^{3}H]LOGANIN (**1**) is incorporated without loss of ^{3}H from the carbon corresponding to C-5 of loganin (hereafter called the *skeletal label*) throughout the biosynthetic steps leading to all three families of indole alkaloids;[1] these are represented by ajmalicine (**7**), catharanthine (**10**), and vindoline (**12**). Vincoside (**3**),[2,3] geissoschizine (**4**),[4,5] and stemmadenine (**5**)[6] are intermediates on the pathway. It is important to determine the location of the skeletal

^{3}H-label for each of the three alkaloidal types in order (*a*) further to test current thinking[7,8] about the mechanisms whereby the *Corynanthé* skeleton of (**4**) is rearranged to the *Strychnos* [*e.g.* (**6**)] *Iboga* [*e.g.* (**10**)] and *Aspidosperma* [*e.g.* (**12**)] skeletons and (*b*) to probe the mechanism whereby vincoside (**3**) is converted into geissoschizine† (**4**).

[5-^{3}H]Loganin[10] administered to *Vinca rosea* plants yielded radioactive ajamalicine (**7**), catharanthine (**10**), and vindoline (**12**); incorporations were 0·2, 1·2, and 0·82%, respectively. Radiochemical purity was established in each case by recrystallisation to matching constant molar activity of the alkaloid and a derivative (or two derivatives) as follows: ajmalicine, alkaloid and picrolonate; catharanthine, hydrochloride and hemitartrate; vindoline, alkaloid and desacetylvindoline (**13**).

Dehydrogenation of ajmalicine (**7**) with mercuric acetate[11] afforded dehydroajmalicine which was crystallised as the perchlorate (**8**) to constant activity and then reduced with borohydride The recovered ajmalicine (**7**) carried 0·2% of the original activity in agreement with ^{3}H-labelling at C-3.

Oxidation of the labelled catharanthine (**10**) with iodine–sodium bicarbonate[12] gave a neutral lactam, $C_{21}H_{22}N_2O_3$, m.p. 231—232°, shown by i.r., n.m.r., and mass spectrometry to have structure (**11**); in particular, the alternative structure involving oxidation at C-5 of (**10**) was excluded. The lactam carried 5·3% of the starting activity and since exchange will not occur from the bridgehead C-14 position under the reaction conditions, it follows that 95% of the original ^{3}H was located at C-3.

Chromium trioxide–pyridine converted vindoline into a mixture of products yielding three pure components, one of which was shown to have structure (**14**). This product, $C_{25}H_{30}N_2O_7$, showed an i.r. band at 1643 cm^{-1} (saturated δ-lactam), absence of olefinic protons at C-14 and -15 by n.m.r., irradiation at τ 5·66 (C-15 H) caused simplification of the τ 7·0—7·8 region to reveal two doublets 7·18 and 7·54 (J 18 Hz) arising from the geminal C-14 protons, mass spectrum m/e 470 (M^+) and three intense ions at 188, 187, and 174 which were also present in the spectrum of vindoline (**12**). When the [^{3}H]vindoline was converted into (**14**), the lactam retained 4·7% of the original activity.

The sequences (**1**) → (**2**) → (**3**) → (**4**) → (**7**) and (**4**) → (**5**) → (**9**) → (**10**) and (**12**) require the [5-^{3}H]-label of loganin (**1**) to appear at C-3 of the alkaloids (**7**), (**10**), and (**12**). Our results establish C-3 labelling for (**10**) and (**12**) and if *total* exchange from C-14 during (**7**) ⇄ (**8**) is excluded,[13] they also do so for (**7**). Further support is thus given to the foregoing biosynthetic sequences and it is established that no hydrogen migration occurs from the carbon corresponding to C-5 of loganin (**1**) and vincoside (**3**) (equivalent to C-3 of the alkaloids) during all the subsequent biochemical rearrangements.

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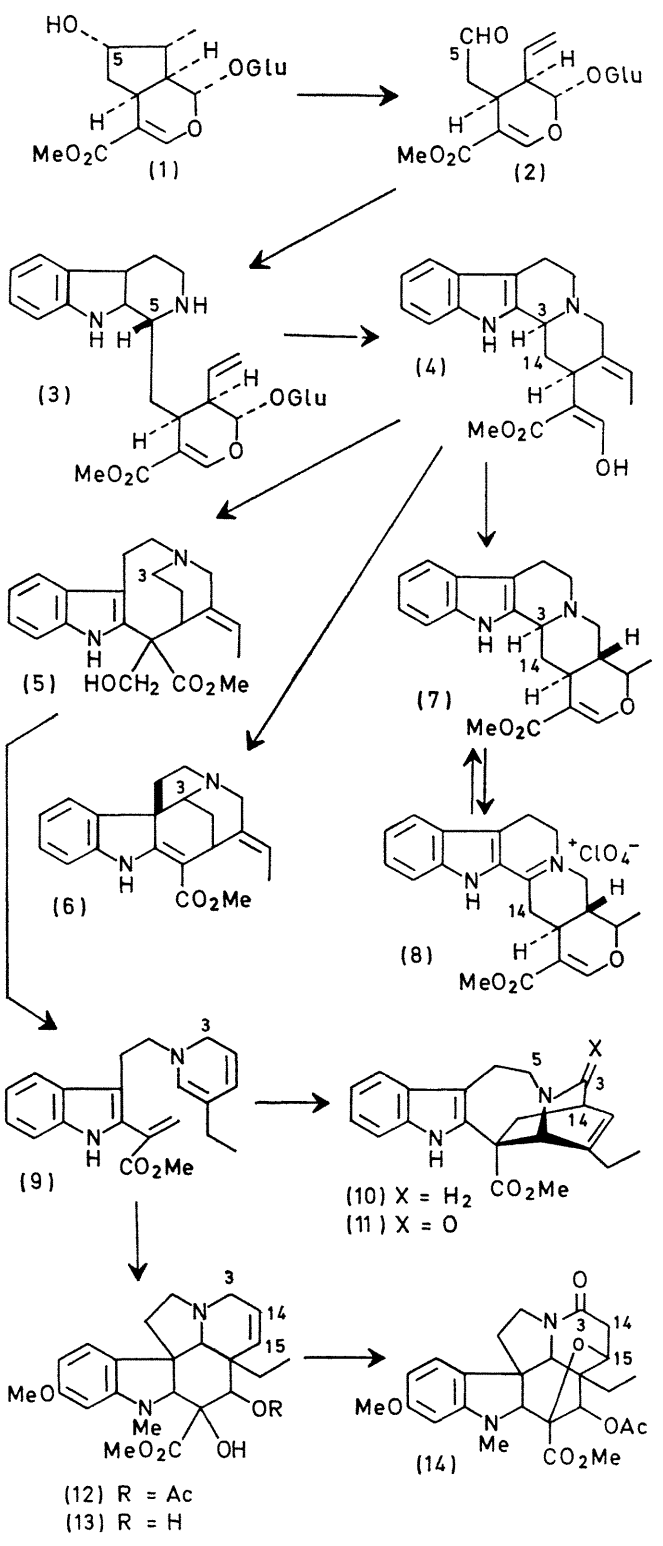

† The illustrated C-3 α-hydrogen of geissoschizine (**4**) rests upon chemical correlation[9] with corynantheidine; X-ray analysis of geissoschizine is being undertaken to provide an independent configurational assignment.

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