Role of Loganin in the Biosynthesis of Indole Alkaloids

By A. R. BATTERSBY, R. T. BROWN, R. S. KAPIL, J. A. MARTIN, and A. O. PLUNKETT

(Robert Robinson Laboratories, University of Liverpool)

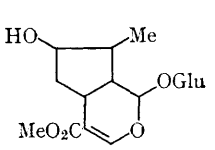
THE suggestion[1] that indole alkaloids are biosynthesised from a cyclopentane monoterpene skeleton (X)* has been strongly supported by feeding experiments with sodium mevalonate and geraniol labelled at various positions.[2] In particular, a bond has been shown[2a] to be formed between carbons C-4 of the two mevalonate units in keeping with ring-closure of geraniol to a cyclopentane system (see X); direct evidence has, however, been lacking. The present Communication reports work in this area.

For reasons discussed elsewhere,[3] loganin[4] (XIV) was selected from the many known cyclopentanoid monoterpenes as the most probable precursor of the indole alkaloids, other possibilities being monotropeine[5] methyl ester (XV; R = Me), verbenalin[6] (XVI), and genepin[7] (XVIII). Verbenalin was labelled by base-catalysed exchange with tritiated water and part of the radioactive material was reduced with borohydride to dihydroverbenalin (XVII). Both substances were ineffective as precursors of the indole alkaloids in *Vinca rosea*. Monotropeine (XV; R = H) was methylated with diazomethane in the presence of tritiated water to yield the ester (XV; R = Me) labelled at the methyl group. The plants fed with this substance gave radio-inactive catharanthine (I), vindoline (II; R = Ac), serpentine (IV), and ajmalicine (V). This result not only makes it very improbable that the monotropeine system (XV) is the correct cyclopentane unit for biological conversion into the indole alkaloids but it also shows that the labelled methyl group is not transferred into the general methylating system of the plant. Accordingly, loganin was hydrolysed to the corresponding loganic acid[4] which was methylated as for monotropeine. The resultant [*O-methyl*-^{3}H] loganin was administered to *Vinca rosea* plants to yield radioactive alkaloids, catharanthine (I; 0·8% incorp.), vindoline (II; R=Ac; 0·5% incorp.), perivine (III; 0·1% incorp.), serpentine (IV; 0·45% incorp.), and ajmalicine (V; 0·026% incorp.). Ziesel demethylation of (I; C_{9-10} unit XII), (IV; C_{9-10} unit XI) and (V) proved all the radioactivity (100%, 109%, and 103%, respectively) to be located at the ester methyl group. Importantly, vindoline (II; R = Ac; C_{9-10} unit XIII) by hydrolysis yielded desacetylvindoline (II; R = H; 98% of original activity) and this by reduction with lithium aluminium hydride[8] gave the diol (II; R = H; CH_2OH in place of CO_2Me). Less than 0·1% of the original activity was retained in the diol proving the label to be located at the ester methyl group; no significant amount was present in the *N*-methyl or aryl *O*-methyl groups. This result eliminates general methyl transfer and is in agreement with specific incorporation of loganin (XIV) into the *Iboga*, *Aspidosperma*, and *Corynanthe* families of alkaloids. Though experiments with multiply-labelled loganin are required to prove rigorously the intact biological conversion of the loganin system into indole alkaloids, we

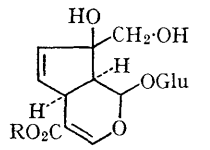
* One set of formulae is used for this and the preceding Communication.

consider the present combined evidence to be strongly in support of this.

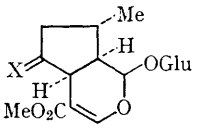
The presence of loganin in *Vinca rosea* plants was tested by radiochemical dilution. Plants fed for 9 days with [1-^{3}H]geraniol were extracted in the presence of radio-inactive loganin. The loganin was then re-isolated as the penta-acetate. Hydrolysis of this product and methylation of the resultant acid afforded loganin of constant specific activity (corresponding to 0·02% incorp.). Conversion again into the penta-acetate and rigorous further purification caused no change in specific activity. This finding that loganin is present in *V. rosea* plants complements the foregoing tracer experiments. Work with multiply-labelled loganin is in progress.



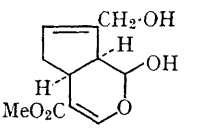
(XIV)



(XV)



(XVI, X=O)
(XVII, X=H, OH)



(XVIII)

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[2] (*a*) Preceding Communication and (*b*) refs. cited there.
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