# Biosynthesis of Loganin and the Indole Alkaloids from Hydroxygeraniol–Hydroxynerol

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*Summary* Tracer experiments on *Vinca rosea* indicate that the conversion of geraniol and nerol into loganin and the indole alkaloids involves 10-hydroxylation as the primary step.

DEOXYLOGANIN (I) is the immediate precursor[1] of loganin (II) and previous work[2,3] proved that geraniol (VII) stands at an earlier stage on the pathway. Nerol (X) is almost as effective a precursor of loganin as geraniol.[4] The conversion of (VII) and (X) into the $C_{10}$-skeleton of (I) involves, in unknown sequence, oxidation of the C-9 and C-10 methyl groups, oxidation of C-1 to the aldehydic state, saturation of the $\Delta^2$-olefinic residue and formation of the cyclopentane ring. The isolation of monoterpenes oxidised at C-10 from *Menyanthes trifoliata*,[5,6] a plant rich in loganin, indicated that oxidation at C-10 might be the primary step. Accordingly, 10-hydroxygeraniol (VIII), 10-hydroxynerol (XI), and the 10-oxygenated (±)-citronellol derivatives (XIV), (XV), and (XVI) were synthesised in labelled form for test as precursors beyond the geraniol stage; also, (±)-citronellal (XIII) and (±)-citronellol (XIII; $CH_2OH$ replaces CHO) were included in the survey Since one of the $^3$H-labels at the chiral centre of [1-*RS*-$^3H_2$]geraniol is incorporated without loss into loganin and into all three types of indole alkaloids,[7] it follows that [1-$^3$H]-labelling can be used with confidence in the present work.

Treatment of dehydrolinalool[8] (III) with alkaline deuterium oxide and Lindlar hydrogenation of the product gave [1-$^2$H]linalool (IV), shown by n.m.r. to be specifically labelled. Repetition of the sequence with tritiated water afforded [1-$^3$H]linalool (IV) which was *O*-acetylated before oxidation by selenium dioxide (*cf.* ref. 9). Reduction of the oxidation products with lithium aluminium hydride gave mainly the diol† (V), characterised as the mono-3,5-dinitrobenzoate m.p. 53—54°. Phosphorus tribromide in ether[10] converted (V) into the dibromide which, by treatment with tetraethylammonium acetate followed by alkaline hydrolysis, gave a mixture of the [1-$^3$H]-diols (VIII) and (XI) in proportion 3·8 : 1 [by g.l.c. and n.m.r.]. The configuration about the $\Delta^7$-bond in (VIII) and (XI) was examined by oxidising the mixture mildly with manganese dioxide.[11] N.m.r. analysis of the major fraction so formed showed it to

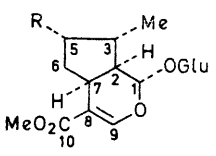
*Tracer experiments on* Vinca rosea

| Precursor | Incorporations (%) Loganin (II) | Ajmalicine (XIX) | Serpentine (XX) | Vindoline (XXI) | Catharanthine (XXII) | Perivine (XXIII) |
|---|---|---|---|---|---|---|
| [1-$^3H_2$]-(VIII) and-(XI)[a] .. | 0·31 | 0·36 | 0·20 | 0·25 | 0·36 | 0·021 |
| [1-$^3H_2$]-(IV)[b] .. .. .. | <0·003 | 0·0 | 0·0007 | 0·0006 | 0·0008 | 0·0001 |
| [1-$^3H_2$]-(XV)[a] .. .. .. | <0·024 | <0·001 | <0·0025 | 0·017 | 0·020 | 0·0006 |
| [1-$^3H_2$]-(XVI)[b] .. .. .. | | <0·005 | <0·0034 | 0·011 | 0·011 | 0·0007 |
| [10-$^3H_2$]-(XIV)[b] .. .. .. | | <0·002 | <0·0048 | 0·048 | 0·032 | 0·0014 |
| [1-$^3H_2$]-Citronellol[b] .. .. | | <0·002[c] | | | | |
| [1-$^3$H]-(XIII)[b] .. .. .. | | 0·0[c] | | | | |

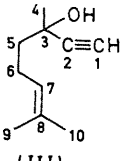
[a] Fed in aqueous solution. [b] Fed as emulsion in aqueous "Tween 80." [c] Expt. by Dr. A. O. Plunkett.

† Full analytical and spectroscopic data in agreement with the assigned structures were obtained for all new compounds.

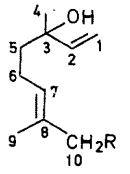
consist of the dialdehydes (IX) and (XII); importantly, only one singlet appeared at $\tau$ 0·53 corresponding to the C-10 proton of the illustrated $\Delta^7$-*trans*-configuration and no signal was present in the $\tau$ −0·1 region where resonance from the corresponding $\Delta^7$-*cis*-isomers would occur.[11] The minor fraction from the oxidation consisted of partially oxidised aldehydo-alcohols (by n.m.r.).



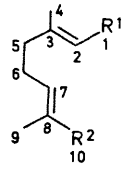
(I) R = H
(II) R = OH

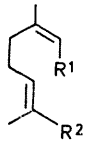


(III)

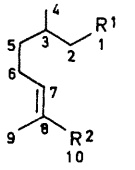


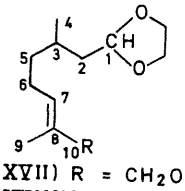
(IV) R = H
(V) R = OH
(VI) R = O–COC$_6$H$_3$(NO$_2$)$_2$





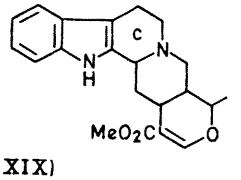
(VII) R$^1$ = CH$_2$OH, R$^2$ = CH$_3$
(VIII) R$^1$ = CH$_2$OH, R$^2$ = CH$_2$OH
(IX) R$^1$ = CHO, R$^2$ = CHO
(X) R$^1$ = CH$_2$OH, R$^2$ = CH$_3$
(XI) R$^1$ = CH$_2$OH, R$^2$ = CH$_2$OH
(XII) R$^1$ = CHO, R$^2$ = CHO



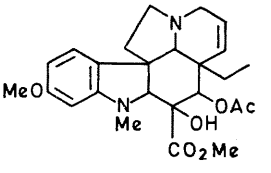


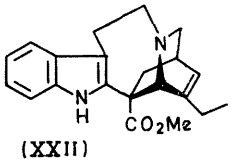
(XIII) R$^1$ = CHO, R$^2$ = CH$_3$
(XIV) R$^1$ = CHO, R$^2$ = CH$_2$OH
(XV) R$^1$ = CH$_2$OH, R$^2$ = CH$_2$OH
(XVI) R$^1$ = CH$_2$OH R$^2$ = CHO

(XVII) R = CH$_2$OH
(XVIII) R = CHO

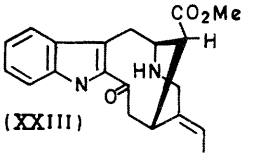


(XIX)
(XX) Ring C aromatised





(XXII)



(XXIII)

Borohydride reduction of (±)-citronellal afforded (±)-[1-$^3$H]citronellol which by Oppenauer oxidation was converted into (±)-[1-$^3$H]citronellal (XIII).

The Table collects the incorporations found for loganin and the alkaloids and the figures have been corrected for loss of 50% of the tritium from C-1 in the [1-$^3H_2$] labelled cases and the expected loss of 75% from C-10 in the (10-$^3H_2$] case. Only with hydroxygeraniol–hydroxynerol (VIII) and (XI) are the incorporations good and comparable to, or higher than, those from geraniol under similar conditions.[2,3,13] Support is thus given to the view that hydroxylation at C-10 of the geraniol–nerol system is the first step in the biological conversion of (VII) and (X) into loganin. The very low incorporation values consistently found from (IV), (XV), (XVI), (XIV), (XIII) and (XIII; $CH_2OH$ replaces CHO) make it improbable that these monoterpenes stand on the direct biosynthetic pathway to loganin. Accordingly, it seems likely that a further step involves oxidative attack at C-9 of (VIII) and (XI), or of the related aldehydes.[14] This possibility can be tested experimentally.

Complementary results based on a different position and method of labelling are reported in an accompanying communication by Prof. Arigoni and his co-workers.

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