Biosynthesis of the Lythraceae Alkaloids: Mode of Incorporation of Phenylalanine

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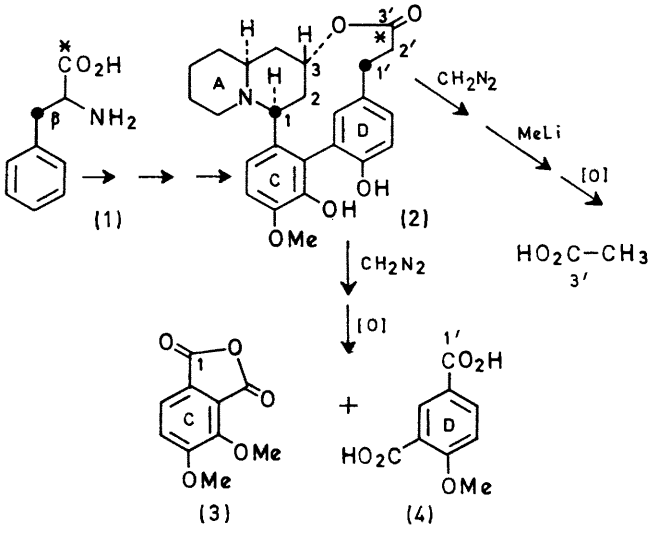
Summary Two fragments derived from phenylalanine (**1**), one a C_6–C_3 unit, the other probably a C_6–C_1 unit, are incorporated into the Lythraceae alkaloid, decodine (**2**).

Activity from [β-^{14}C]phenylalanine (**1**) enters the two predicted positions (●) of the phenylquinolizidine alkaloid cryogenine[1] [an isomer of *O*-methyl-1′,2′-dehydro-(**2**)]. This observation was consistent with the four hypotheses,[1–3] summarized in ref. 4, which have been advanced to account for the origin of this group of alkaloids, but did not distinguish among them. In all these hypotheses an intact C_6–C_3 unit, derived from phenylalanine *via* cinnamic acid, supplies ring D and the adjacent C_3 chain (C-1′,-2′,-3′). One of the questions, which remains unresolved, is whether ring C and the three carbon atoms, C-1,-2,-3, originate as a unit from a similar C_6–C_3 moiety,[1–3] or whether it is a phenylalanine-derived C_6–C_1 unit which generates the C_6–C_1 fragment, ring C plus C-1, of the alkaloids, leaving C-2 and C-3 to be contributed by a different precursor.[1] We now offer evidence which favours the latter alternative.

A sample of [carboxyl,β-$^{14}C_2$]-(±)-phenylalanine of known isotope distribution (Table), prepared by mixing [carboxyl-^{14}C]-(±)-phenylalanine (*ca.* 0·1 mCi) and [β-^{14}C]-(±)-phenylalanine (*ca.* 0·1 mCi), was administered to plants of *Decodon verticillatus* (L.) Ell.



The alkaloid fraction, isolated[5] from these plants, was radioactive. Decodine (**2**), the major alkaloid, was purified to constant radioactivity (0·04% incorporation), converted into the *OO*-dimethyl derivative and then degraded to

separate predicted sites of radioactivity. Treatment with methyl-lithium followed by Kuhn–Roth oxidation gave carbon chain of phenylalanine into the phenylpropanoid unit of the alkaloid is demonstrated.

TABLE

Incorporation of [1,3-$^{14}C_2$]*phenylalanine into decodine*

Precursor	Relative specific activity (%)	Product	Relative specific activity (%)
[Carboxyl,β-$^{14}C_2$]-(±)-phenylalanine ..	100 ± 1·6	Dimethyldecodine	100 ± 1·3
		Hemipinic anhydride (**3**) (C-1) ..	46·4 ± 1·2
β-^{14}C	54·6 ± 1·3	4-Methyoxyisophthalic acid (**4**) (C-1′)	26·6 ± 0·6
Carboxyl-^{14}C	45·4 ± 1·4	Kuhn–Roth Acetate (C-3′)	21·8 ± 0·6
		Recovered in degradation products ..	94·8 ± 1·5%
$\frac{\beta\text{-}^{14}C}{\text{carboxyl-}^{14}C} = 1{\cdot}20 \pm 0{\cdot}05$		$\frac{\text{4-Methoxyisophthalic acid (C-1′)}}{\text{Kuhn–Roth acetate (C-3′)}} = 1{\cdot}22 \pm 0{\cdot}04$	

acetic acid, isolated as the α-naphthylamide, representing the carbonyl carbon, C-3′. Permanganate oxidation gave a mixture of products from which hemipinic anhydride (**3**) (containing C-1 as the only carbon atom not originating from an aromatic nucleus) and 4-methoxyisophthalic acid (**4**) (containing C-1′ as the only "non-aromatic" carbon) were isolated and rigorously purified.

The relative specific activity of each of these degradation products is shown in the Table. The three products account for almost the entire activity of the intact alkaloid. Of this activity, 49% is located within the C_6–C_3 unit, ring D, C-1′,-2′,-3′. Since the distribution of label within this unit (C-1′ : C-3′ = 1·22 ± 0·04) is identical, within experimental error, to the distribution of ^{14}C within the precursor (β : carboxyl = 1·20 ± 0·05), and since label at C-1′ in a closely related alkaloid is known to be derived from the β-carbon of the precursor,[1] intact incorporation of the

The rest of the activity of the alkaloid (46%) is confined to C-1 of the quinolizidine nucleus, a site known[1] to be derived from the β-carbon of phenylalanine. It is evident that whereas the β-carbon of the precursor enters two carbon atoms, C-1 and C-1′, of the alkaloid, the carboxyl carbon enters only one site of the product, the carbonyl carbon of the phenylpropanoid moiety. It follows that the phenylalanine-derived moiety which enters the phenylquinolizidine system of the alkaloid cannot be an intact C_6–C_3 unit.

Even though the possibility is still open that a C_6–C_2 unit enters this system,† the present results, together with earlier evidence[4] on the derivation of ring A of decodine from lysine, are entirely consistent with the hypothesis[2] that the phenylquinolizidine system is generated by combination of a phenylalanine-derived C_6–C_1 unit with a pelletierine moiety.

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† It should be noted, however, that phenolic C_6–C_2 units which are implicated in the biosynthesis of secondary plant substances appear to be invariably derived from tyrosine, whereas phenolic C_6–C_1 and C_6–C_3 units are always supplied by phenylalanine.

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