

## Biosynthesis of Aristolochic Acid

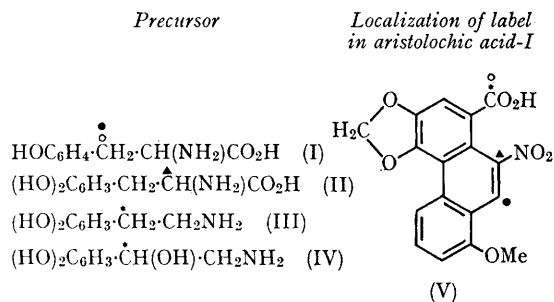
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THE aristolochic acids (*e.g.*, V),<sup>1,2,3</sup> derivatives of 10-nitro-1-phenanthroic acid, occur in various species of the genus *Aristolochia*. The striking structural kinship of their skeleton with that of the aporphine alkaloids suggests a biogenetic relationship.<sup>1</sup> If the nitro- and the carboxyl group of the acids were indeed metabolic relics of the heteroring of an aporphine system, the acids would be a further group of natural products related to norlaudanosoline.<sup>4,5</sup> We now report results which are consistent with such a biosynthetic relationship.

We have studied the biosynthesis of aristolochic acid-I (8-methoxy-3,4-methylenedioxy-10-nitro-1-phenanthroic acid) (V) in *Aristolochia siphon* (syn. *A. durior*).<sup>6</sup> In separate experiments a number of <sup>14</sup>C-labelled compounds were administered to intact plants by infusion into the stem through a cotton wick,<sup>4</sup> and in each case radioactive aristolochic acid-I was then isolated from roots and rhizomes. Decarboxylation of the acid to the corresponding nitrophenanthrene derivative permitted assay of radioactivity at the carboxyl group. Aristolochic acid-I, derived from [3-<sup>14</sup>C]-DL-tyrosine (I) (0.01% incorporation) lost more than 60% of its activity on decarboxylation. There was no loss of activity when aristolochic acid-I, derived from [2-<sup>14</sup>C]-DL-dihydroxyphenylalanine (II) (0.02% incorporation), was decarboxylated. Decarboxylation of the acid, derived from [2-<sup>14</sup>C]-dihydroxyphenylethylamine (III) (0.02% incorporation), gave an inactive sample of the corresponding nitrophenanthrene. These results, summarized in the Figure, indicate a distribution of label which corresponds to that expected if norlaudanosoline were an intermediate of the biosynthetic pathway from the administered precursors to the product, and they are consistent with the postulated<sup>7</sup> route norlaudanosoline → orientaline<sup>8</sup> → orientalinone → orientalinol → stephanine → aristolochic acid-I, which involves a

phenol coupling step and a dienol-benzene rearrangement.



○, • denotes the established sites and  
●, ▲ the probable sites of radiocarbon derived  
from individual precursors

The outcome of a further experiment is difficult to reconcile with this route. Aristolochic acid-I, derived from [2-<sup>14</sup>C]-DL-noradrenaline (IV) (0.1% incorporation), was labelled exclusively at the carboxyl carbon. This result provides a second instance of specific incorporation of noradrenaline into a plant product.<sup>9</sup> Even though this evidence does not prove that noradrenaline is an obligatory intermediate of the biosynthetic pathway, it is nevertheless enticing to speculate that the aristolochic acids are related to 4-hydroxynorlaudanosoline, rather than to norlaudanosoline, and that it

is the presence of a benzylic hydroxyl group which predisposes an aporphine intermediate to oxidative

conversion into an aristolochic acid.

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<sup>6</sup> Dr. R. W. Doskotch, Ohio State University, Columbus, informs us that an independent study of aristolochic acid biosynthesis is in progress in his laboratory.

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