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THE BIOSYNTHESIS OF THE PHENETHYLISOQUINOLINE ALKALOID, COLCHICINE, FROM CINNAMALDEHYDE AND DIHYDROCINNAMALDEHYDE

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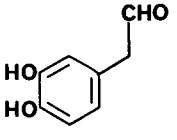
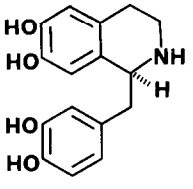
Summary: The important phenethylisoquinoline alkaloid, colchicine (10) is shown to derive from cinnamic acid (5) via cinnamaldehyde (6) and dihydrocinnamaldehyde (7); dihydrocinnamic acid (4) may be used by a minor pathway.

In important recent work it has been shown that benzylisoquinoline alkaloids, which are elaborated via reticuline, are biosynthesized by condensation of the aldehyde (1) with dopamine (8) to give (S)-norlaudanosoline (2).[1] In this the biosynthesis resembles that of the 1-phenylisoquinoline,[2] ipecac,[3] and terpenoid indole[4] alkaloids where similar ring formation occurs by condensation of an amine with an aldehyde. By contrast the simple isoquinolines, e.g. anhalonidine,[5] and the ß-carboline alkaloids, e.g. eleagnine,[6] are formed by condensation of an amine with an α-keto-acid. The important and unusual alkaloid colchicine (10) is one of a small group of phenethylisoquinolines [as (9)]. We report here evidence which establishes that the biosynthesis of the phenethylisoquinoline skeleton involves condensation of an aldehyde [i.e. (6)/(7)] with an amine [i.e. dopamine (8)].



(1)



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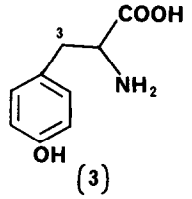

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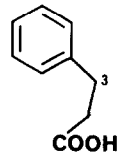


(4)

The tropolone ring of colchicine (10) is formed from the aromatic nucleus of tyrosine (3) plus C-3 by way of dopamine (8).[7,8] Ring A of (10) together with C-5, -6, and -7 derive from phenylalanine by way of cinnamic acid (5).[8,9] Beyond cinnamic acid, negative results with oxygenated derivatives suggested that reduction of the double bond in cinnamic acid occurs before oxygenation of the aromatic ring.[8] We have examined this possibility as well as whether the cinnamic acid derivative that combines with dopamine is at the aldehyde or at the acid level of oxidation in feeding experiments with a mixture of [3-^{14}C]cinnamic acid [as (5)] and [1-^{3}H]-cinnamaldehyde [as (6)][10] and a mixture of [3-^{14}C]dihydrocinnamic acid [as (4)] and [1-^{3}H]dihydrocinnamaldehyde [as (7)].[10] The experiments were carried out with corms of Colchicum byzantinum during this last autumn's flowering period.

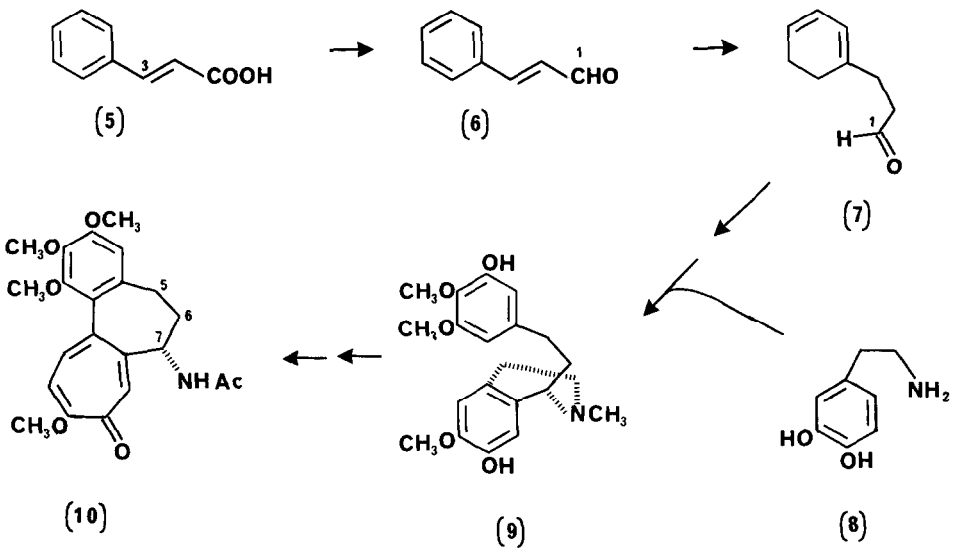
The following is to be noted: (1) mixtures of precursors, where one compound bore a ^{14}C-label and the other a ^{3}H-label, were used in order to provide the most accurate comparison of incorporation efficiencies by testing the incorporation in the same plants; (2) the aldehydes were deliberately labelled with tritium on their carbonyl groups so that incorporation would only be observed if the aldehyde function did not suffer oxidation (to a carboxylic acid) during biosynthesis; (3) because of their insolubility in water the two aldehydes were fed as aqueous solutions of their bisulphite addition compounds. As can be seen (Table) the strategy of using the bisulphite-addition compounds of (6) and (7) was successful and this is potentially applicable in other biosynthetic experiments involving aldehyde precursors.

After each of the two experiments the colchicine (10) was isolated and recrystallized to constant radioactivity. H.P.L.C. analysis of the residues obtained in each experiment gave many non-polar, radioactive components but no radioactive alkaloid other than colchicine was obtained.

It can be seen from the Table that the ^{3}H:^{14}C ratio of the precursor mixture in experiment 1 is closly similar to the ratio in the isolated colchicine. This indicates that cinnamic acid and cinnamaldehyde are equally good precursors for colchicine (10); retention of tritium shows that biosynthesis is from cinnamic acid *via* cinnamaldehyde. The results of experiment 2 show that dihydrocinnamaldehyde is incorporated at a similar level to the precursors in experiment 1, and that it is a significantly better precursor than dihydrocinnamic acid. The level at which this acid was incorporated indicates that it may be utilized by a minor pathway *via* (5)

Table: Incorporation of precursors into colchicine (10).

Expt.	Precursor	Colchicine isolated % incorp.	$^{3}H:^{14}C$
1	[1-^{3}H]cinnamaldehyde (110 μCi)	0.10	3.8
	+ [3-^{14}C]cinnamic acid (25 μCi)	0.12	
	$^{3}H:^{14}C$ = 4.4		
2	[1-^{3}H]dihydrocinnamaldehyde (110 μCi)	0.08	8.8
	+ [3-^{14}C]dihydrocinnamic acid (25 μCi)	0.04	
	$^{3}H:^{14}C$ = 4.4		



Scheme

or (7). Together the results lead to the pathway shown in the Scheme; it remains to be established whether (7) is an obligatory intermediate between (6) and (9). Experiments which further delineate the biosynthetic pathway to phenethylisoquinoline alkaloids are in hand. In a preliminary way we have obtained a 0.07% incorporation of DL-[2-^{14}C]phenylalanine into colchicine (10) using fresh tissue slices of C. byzantinum.

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