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BIOSYNTHETIC DERIVATION OF HASUBANONINE AND PROTOSTEPHANINE FROM THE 1-BENZYLISOQUINOLINE SYSTEM

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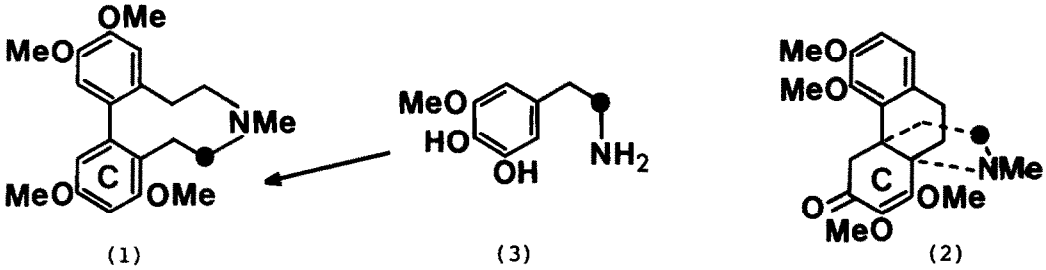
Few alkaloids have been more recalcitrant in yielding positive information concerning their biosynthesis than have protostephanine (1) and hasubanonine (2) and this secrecy increased their fascination. Already in the late nineteen sixties, tracer experiments on the parent plant, Stephania japonica Miers, had given positive incorporations of labelled tyrosine [1] into the alkaloids. Degradation showed [2] that both skeletons (1) and (2) are built from two Ar-C-C units derivable from tyrosine. During the following years, many labelled 1-benzylisoquinolines were synthesised which on biogenetic grounds could be possible late precursors of (1) and (2) but none was significantly incorporated by the living plant into either alkaloid.[2]



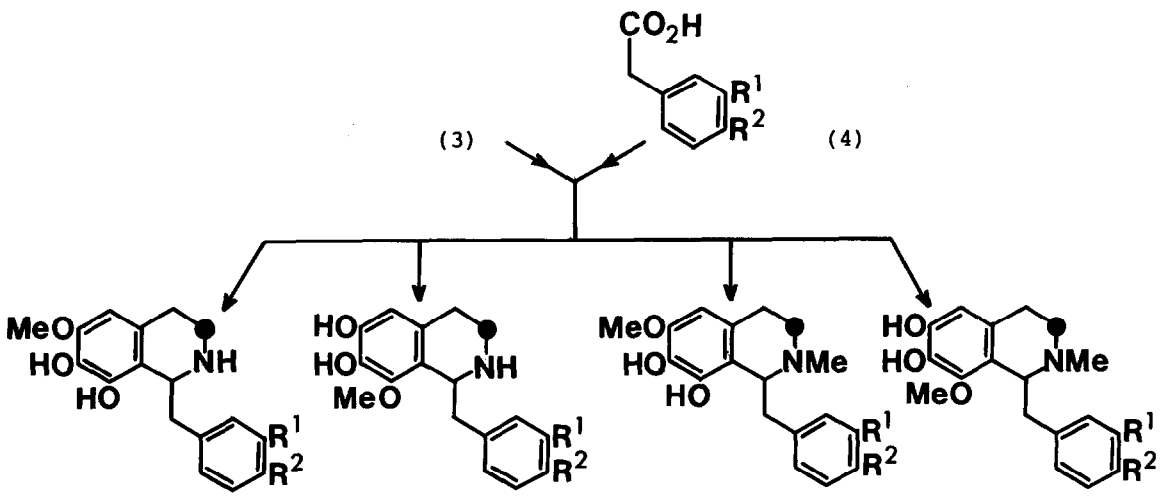
(1) (3) (2)

Accordingly, a logical study was made of how the plant modifies the simple Ar-C-C units before slotting them into protostephanine (1) and hasubanonine (2). As a result it was discovered [2] that ring-C and the attached ethanamine chain of (1) and (2) are derived in vivo from the diphenolic base (3); neither of the dimethoxy monophenols derived from (3) acted as precursors of the alkaloids.[2]

The way was then open to synthesise the set of 1-benzylisoquinolines in the illustrated labelled form (Scheme 1) which can be built from the protected amine (3) and an acid component carrying a systematically varied oxygenation pattern (4a-d). Two main series of compounds (5a-d) and (6a-d) were prepared by standard sequences and their N-methyl analogues (7a-d) and (8a-d) were included in the study†.

† In addition, the four possible bisphenethylamines $ArCH_2CH_2NHCH_2CH_2Ar'$ derived from (3) and the series (4a-d) were synthesised but none acted as precursor of (1) or (2) in S. japonica.

These sixteen labelled bases were administered separately to vigorously growing young S. japonica plants, (1) and (2) were then isolated and the Table shows the six precursors which were well incorporated into the alkaloids. Degradation as earlier [2] of the hasubanonine (2) from Experiments 2, 3 and 7 located the label entirely on the ethanamine bridge so establishing specific incorporations. All the results are self-consistent and they accord with a branching pathway illustrated in Scheme 2; it is interesting that the timing of N-methylation is not critical.



(5) (6) (7) (8)

(a) R^1 = H, R^2 = OH (c) R^1 = OMe, R^2 = OH

(b) R^1 = R^2 = OH (d) R^1 = OH, R^2 = OMe

Scheme 1

It is thus established that protostephanine (1) and hasubanonine (2) are "disguised" members of the 1-benzylisoquinoline group and the actual precursors now pin-pointed are subtlely modified derivatives of those which feature in earlier speculations.[3] As far as we know, the cases here are unique in requiring two phenolic hydroxyl groups in one of the rings undergoing oxidative coupling (Scheme 2).

The synthesis of dienones (9) and (10) is in progress for studies of their chemistry and to allow tests of their efficacy, respectively, as advanced precursors of the protostephanine (1) and hasubanonine (2) systems.

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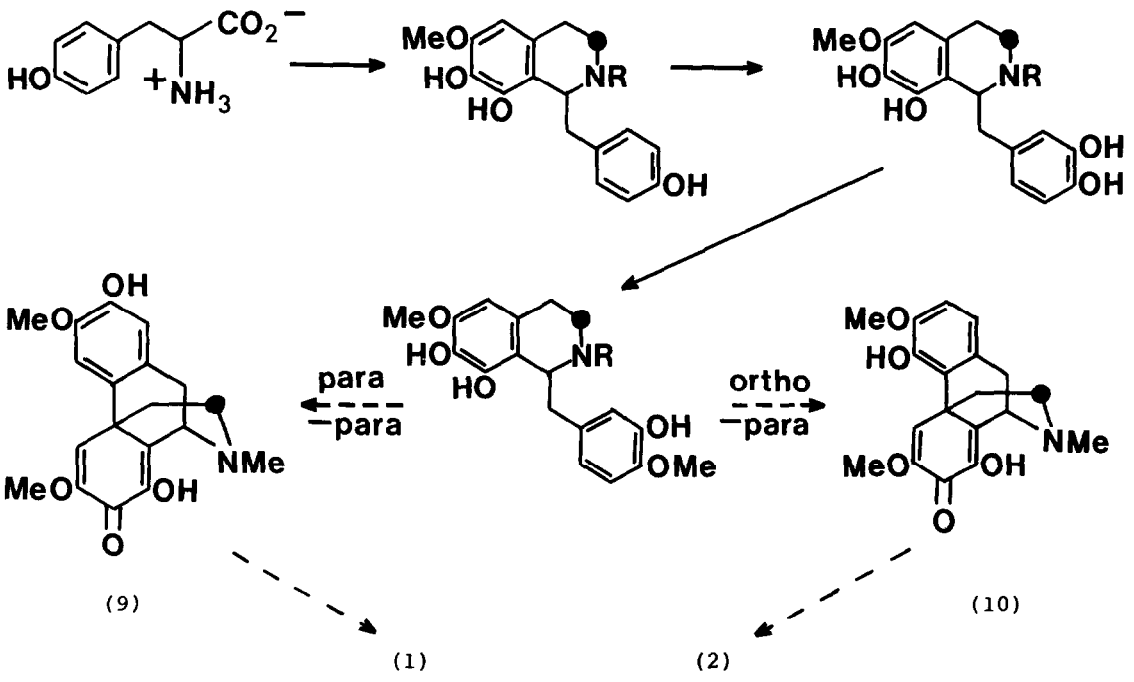
TABLE Tracer Experiments on Stephania japonica

Expt. No.	Precursor	% Incorp. into (1)	% Incorp. into (2)	% Label in bridge of (2)
1	2RS-[2-^{14}C]Tyrosine	0.1	1.2	57±1
2	(5a)	0.020	0.35	100±1
3	(5b)	0.022	0.33	100±1
4	(5d)	0.017	0.24	¶
5	(7a)	0.022	0.43	¶
6	(7b)	0.023	0.25	¶
7	(7d)§	0.005	0.10	98±1

§ Isolation difficulties necessitated considerable dilution with unlabelled material for this product; the size of the positive and specific incorporation requires redetermination.

¶ Not determined.



Scheme 2 R = H or Me

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