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# EXPERIMENTS ON THE EARLY STEPS OF MORPHINE BIOSYNTHESIS

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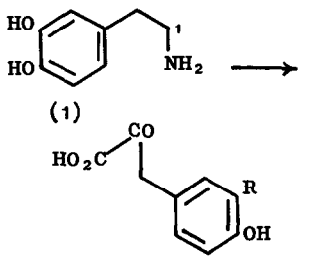
Earlier work[1-4] has defined with considerable precision how the 1-benzylisoquinoline system is converted by opium poppies into the morphine group of alkaloids (13 = morphine). Norlaudanosoline (12) was the earliest 1-benzylisoquinoline recognised[5,11] on this pathway and it was shown to be built from two aromatic units both derivable from tyrosine (10); one of these was dopamine[6] (1). The nature of the second unit is unknown but 3,4-dihydroxyphenylacetaldehyde and the pyruvic acid (2) have featured in speculations.[3] Dopamine (1) reacting with the phenylacetaldehyde would yield norlaudanosoline (12) directly whereas condensation of dopamine with (2) would form the amino acid (4). It is relevant that there is good evidence supporting biosynthesis of 1-methyltetrahydroisoquinoline alkaloids from pyruvic acid.[7] Tracer experiments in Papaver somniferum with the amino acids (4) and (5) and related experiments are now outlined which complement the recent work of Wilson and Coscia[8] with P. orientale latex and seedlings.

Condensation[9] of the pyruvate[10] (2) with [1-$^{14}$C]dopamine (1) at pH 5 gave the (1-RS)-[3-$^{14}$C]amino acid (4, 41% yield) isolated as its hydrochloride; the (1-RS)-[3-$^{14}$C]amino acid[11] (5, 35% yield) was prepared similarly from the keto acid (3). The 3,4-dihydro[3-$^{14}$C]isoquinolines (6) and (8) were synthesised by standard methods (e.g. ref. 4) and were subjected to acid catalysed debenzylation to yield the tetraphenolic (7) and triphenolic (9) 3,4-dihydroisoquinolines.

Incorporation experiments in which solutions of these products were injected into the capsules of intact P. somniferum plants gave results for the isolated morphine collected in the Table; (2RS)-[2-$^{14}$C]-3,4-dihydroxyphenylalanine (11, dopa) was also tested. Degradation of the labelled morphine from Expts. 1 and 5 gave O-acetylmethylmorphol (14) and its radioactivity showed that in each case, essentially all the

$^{14}$C-labelling of the morphine samples was located in the ethanamine bridge [thickened bonds in (13)].

These results, which interlock with those for P. orientale latex,[8] show that (a) the amino acid (4) can act as a specific precursor of morphine (13); only one enantiomer of (4) would be expected to be biologically converted (b) the aromatic nuclei of both building blocks for the 1-benzylisoquinoline system are dihydroxylated before isoquinoline formation occurs (c) the dihydroisoquinoline (7) may lie on the pathway between the amino acid (4) and norlaudanosoline (12), (d) externally introduced [2-$^{14}$C]dopa (11) does not significantly label the pool of the keto acid (2) from which the amino acid (4) is presumably built; one possibility is that in the intact plant, added dopa (11) fails to penetrate to the site of the appropriate aminotransferase.

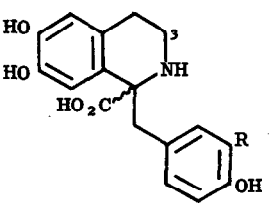


(1)



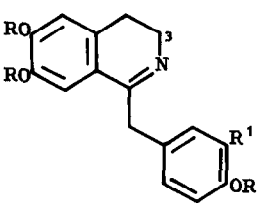
(2) R = OH

(3) R = H



(4) R = OH

(5) R = H

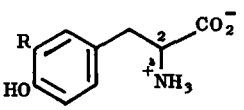


(6) R = $CH_2Ph$, $R^1$ = $OCH_2Ph$

(7) R = H, $R^1$ = OH

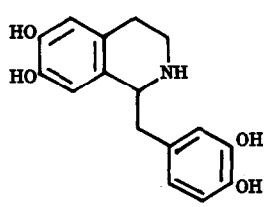
(8) R = $CH_2Ph$, $R^1$ = H

(9) R = H, $R^1$ = H

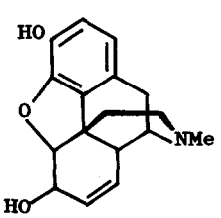


(10) R = H

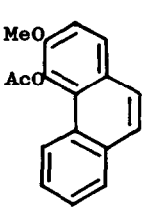
(11) R = OH



(12)



(13)



(14)

Incorporation and trapping experiments with the resolved enantiomers of the amino acid (4) would be of considerable interest.

TABLE Tracer experiments on Papaver somniferum

| Expt. No. | Precursor | % Incorporation into morphine (13) | % Total activity in ethanamine bridge[a] |
|---|---|---|---|
| 1 | [3-$^{14}$C]Amino acid (4) | 0.07 | 99 |
| 2 | [3-$^{14}$C]Amino acid (5) | < 0.007 | b |
| 3 | [3-$^{14}$C]Tetraphenol (7) | 0.07 | b |
| 4 | [3-$^{14}$C]Triphenol (9) | < 0.02 | b |
| 5 | [2-$^{14}$C]Dopa (11) | 0.78 | 97 |

[a] Determined from amount of radioactivity remaining in O-acetylmethylmorphol (14).

[b] Not examined

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