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THE INCORPORATION OF DOPAMINE INTO CHELIDONINE AND MORPHINE

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Recently Spenser and Gear administered dopamine-1-C^{14} (I) to Hydrastis canadensis plants and obtained hydrastine (IV) which was labeled only at C-3 (1,2). On the other hand the radioactive hydrastine which was obtained when tyrosine-2-C^{14} was fed to the plant was labeled at both C-1 and C-3 (2,3). These results may be rationalized by postulating that an intermediate in the biosynthesis of hydrastine is the tetrahydroxybenzylisoquinoline III . This compound could be formed by a Mannich condensation between dopamine and 3,4-dihydroxyphenylpyruvic acid (II) , the carboxyl group being either lost during the condensation or in a subsequent step. Radioactive tyrosine could thus serve as a precursor of dopamine and the keto acid II , resulting in labeling of the two "halves" of the benzylisoquinoline III . Reaction of III with one-carbon precursors ultimately affords hydrastine (4).

It has been shown recently (5,6,7) that morphine (V) is derived from the benzylisoquinoline III or a closely related

compound. We therefore expected that the administration of dopamine-1-C^{14} to Papaver somniferum plants would result in the formation of morphine labeled at C-16 . We have now carried out experiments which confirm our expectations.

Dopamine-1-C^{14} hydrobromide (Purchased from New England Nuclear Corp., Boston, Mass.) (16.4 mg., 2.26 x 10^8 d.p.m.) was administered to ten 3-month-old P. somniferum plants growing in soil (May, 1962) by means of a cotton wick inserted into the stem. After two weeks the alkaloids were extracted from the plants and separated by counter current distribution (8) . Morphine (100 mg.) having a specific activity of 3.8 x 10^6 d.p.m./mM (0.59% incorporation) was obtained. Systematic degradation of this morphine by Battersby's method (8) indicated that essentially all the radioactivity was located at C-16*.

Chelidonine (VII) is another alkaloid which is plausibly derived from the benzylisoquinoline III . We have already shown that the administration of tyrosine-2-C^{14} to Chelidonium majus results in the formation of radioactive chelidonine (9). Degradation of this chelidonine yielded compounds whose activities were consistent with specific labeling at C-4b and C-11. We have now fed dopamine-1-C^{14} hydrobromide (17.6 mg., 2.42 x 10^8 d.p.m.) to three C. majus plants growing out of doors

*We are indebted to Professor A. R. Battersby for friendly discussions in which he informed us that he had independently obtained the same result, cf. reference (5).

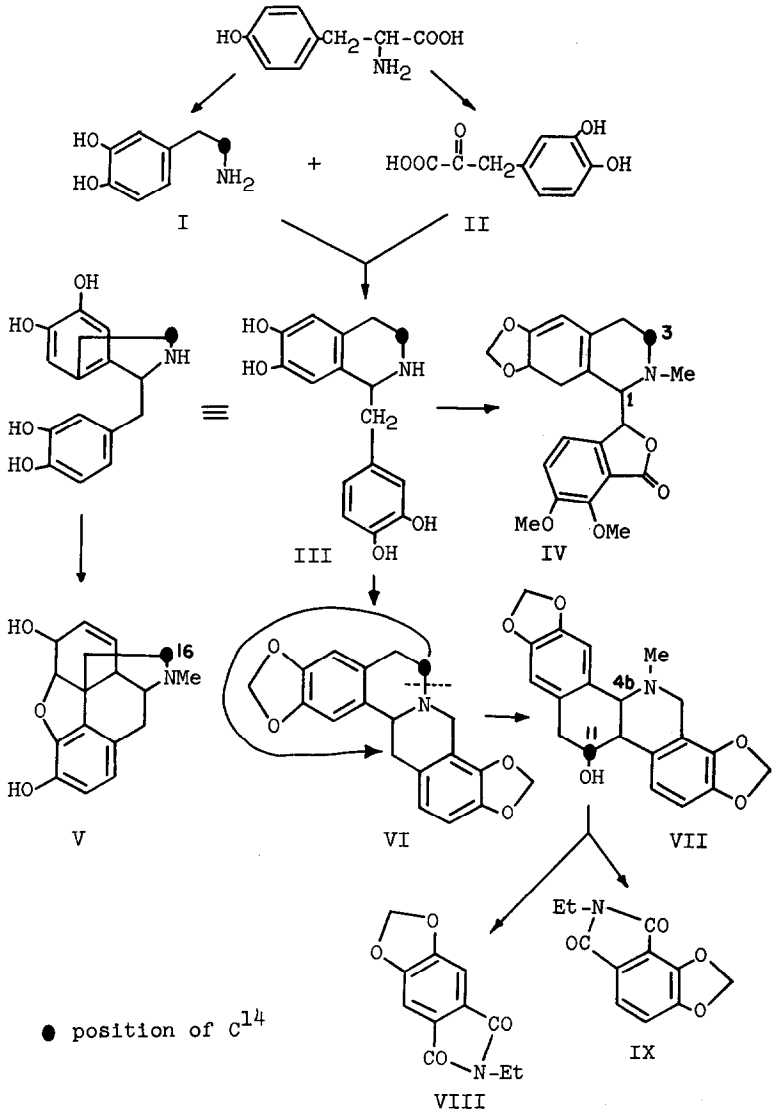
HO
CH2-CH-COOH
NH2
HO
HO
NH2
I
+
HOOC-C-CH2
O
OH
OH
II
OH
HO
HO
NH
HO
HO
HO
HO
NH
CH2
OH
OH
III
O
O
3
N-Me
1
O
O
MeO
OMe
IV
HO
16
NMe
O
HO
V
O
O
N
VI
O
O
Me
4b
N
OH
O
O
VII
Et-N
CO
OC
O
O
O
CO
CO
N-Et
VIII
IX
● position of C14

Figure 1.

(June, 1963) by the wick method. After eight days the alkaloids were isolated and separated as previously described (9). Chelidonine (240 mg.) and its derivatives (hydrochloride, O-acetyl) had a specific activity of 1.35×10^6 d.p.m./mM. (0.38% incorporation). Oxidation of the chelidonine with potassium permanganate yielded hydrastic acid and 3,4-methylenedioxyphthalic acid, which were isolated as their N-ethylimides , VIII and IX respectively. Treatment of the chelidonine with hydriodic acid afforded methyl iodide which was collected as triethylmethylammonium iodide . All of these degradation products had negligible activity ($<0.01 \times 10^6$ d.p.m./mM.) compared with the chelidonine , indicating that all the activity of the alkaloid was located at C-11 . DL-Stylopine* (VI) was also isolated from the C. majus plants which had been fed dopamine-1-C^{14} , and had a specific activity of 3.15×10^6 d.p.m./mM. It is tempting to speculate that chelidonine is formed from stylopine by an appropriate bond fission and rearrangement , indicated schematically in Fig. 1. Work is in progress to test this hypothesis.

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