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CONCERNING THE BIOSYNTHESIS OF NARCOTINE

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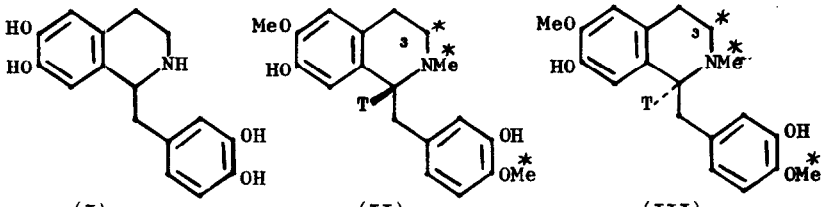
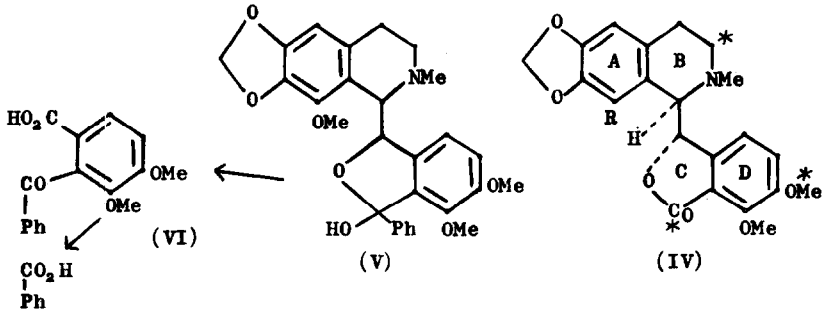
TRACER experiments with [2-^{14}C]tyrosine and, more directly, with [1-^{14}C]norlaudanosoline (I) proved (1) that the biosynthetic route to the phthalideisoquinoline alkaloid narcotine (IV, R=OMe) involves a 1-benzylisoquinoline moiety. It was further demonstrated (1) that the lactone carbonyl group originates from the one-carbon pool, in accord with biogenetic theory (2); however, this experiment gives no information concerning the level of oxidation at which the one-carbon unit enters the alkaloid. We now report the main results from further studies.

[methyl-^{14}C]Methionine fed to Papaver somniferum plants (variety "Schlanstedt") afforded narcotine (0.04% incorp.) which was degraded by conversion (3) first into phenylnarcotine (V). This was oxidised to yield benzoic acid (16.5% of total activity) and the acid (VI) (4) (49.9% of total activity). Formaldehyde (17.6% of total activity) was isolated from the methylenedioxy group by hydrolysis. These results prove that the lactone carbonyl group and the methylenedioxy group (5) arise from the S-methyl group of methionine and one would expect the three O-methyl groups and the N-methyl group also to be so derived; the above results are in agreement with this.

Spenser and his co-workers (6,7) have reported that formate and methionine act as precursors of the methylenedioxy, N-methyl, lactone carbonyl and the two O-methyl groups of hydrastine (IV, R=H); their results and ours are in close agreement.



(I) (II) (III)



(VI) (V) (IV)

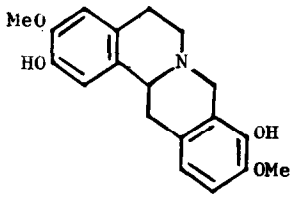
Narcotine (IV, R=OMe) has the illustrated absolute configuration (8-10) which corresponds to that of (+)-reticuline (III). Accordingly, quadruply labelled (-)-reticuline (II) and (+)-reticuline (III), of 96% optical purity, were synthesised with labels as shown (11,12) and fed separately to Schlanstedt poppies. The (+)-isomer (III) was incorporated (0.042%) to a somewhat higher extent into narcotine than was found (0.031%) for (-)-reticuline (II). Incorporation of the "wrong" isomer must occur by racemisation,

possibly by oxidation-reduction as was recently proved for the biosynthesis of morphine (12). In keeping with this, there is considerable loss of tritium in the course of incorporation of both reticulines but we reserve comment on this aspect until after further work. Degradation of the two samples of radioactive narcotine was carried out as above and the activities of the products allow the comparisons in the Table to be made; the Table also shows the way in which values by difference are derived.

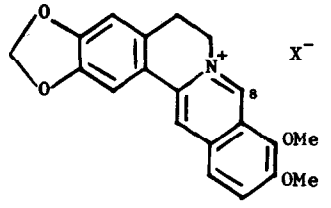
^{14}C-Activities of Precursors and Products

	N-Me	O-Me	C-3
(+)-, and (-)-Reticuline	0.11	0.14	0.75
Degradation Products from Narcotine	$PhCO_2H$	(VI)-$PhCO_2H$	(IV,R=OMe)-(VI)
From (+)-Reticuline	0.11	0.14	0.75
From (-)-Reticuline	0.12	0.13	0.75

The results show the specific incorporation of (+)-, and (-)-reticulines into narcotine and they prove that the lactone carbonyl group is derived from the N-methyl group of reticuline by a process not involving significant fission of the N-methyl bond until after the bond to ring-D has been established. The formation of a protoberberine, probably scoulerine (VII), is



(VII)



(VIII)

an attractive first step and then as earlier envisaged (2), oxidation and N-methylation to yield the phthalideisoquinoline system. It has already been proven that C-8 of berberine (VIII) arises by ring-closure of an N-methyl group (13,14).

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