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A COMPLETE BIOSYNTHETIC SEQUENCE FROM TYROSINE TO MESCALINE IN TWO CACTUS SPECIES.

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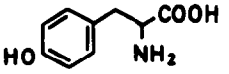
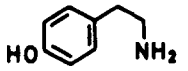
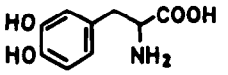
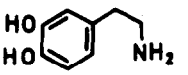
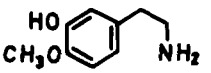
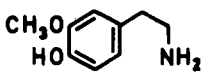
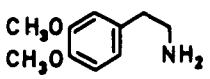
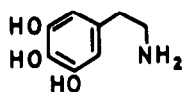
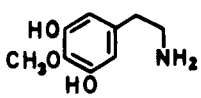
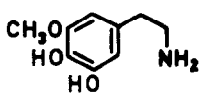
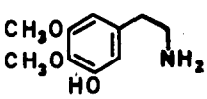
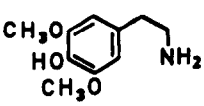
The early steps in the pathway from tyrosine to mescaline in the peyote cactus, Lophophora williamsii Coult., have been reported before (1,2,3). Recently we reported the presence in two different cactus species of methoxylated phenolic alkaloids which could be regarded as possible intermediates in the biosynthesis of mescaline. Thus L. williamsii was found to contain 3,4-dimethoxy-5-hydroxyphenethylamine 11 and from Trichocereus pachanoi Br&R 3-methoxy-4-hydroxyphenethylamine 6 and 3,5-dimethoxy-4-hydroxyphenethylamine 12 were isolated. These findings might suggest a biosynthesis of mescaline from dopamine via 3-methoxy-4-hydroxyphenethylamine 6 to 3,4-dihydroxy-5-methoxyphenethylamine 10 and then further to mescaline (4).

To thoroughly test this hypothesis we synthesized all possible hydroxy and methoxy substituted phenethylamines for use as precursors. The compounds in Table I were labelled with ^{14}C in the α-carbon of the side chain or with ^{3}H in the side chain (5) and were tested as precursors of mescaline in both L. williamsii and T. pachanoi. Experimental details have been described before (1,3). The results of the incorporation experiments are shown in Table I. Some of the earlier results on the incorporations into mescaline in L. williamsii are included for comparision (compounds 1 - 4 and 7 - 8).

The alternative routes from tyrosine to dopamine (Scheme I) in L. williamsii have been reported earlier (1,2). In T. pachanoi tyramine 2 is clearly better incorporated than DOPA 3 and this might indicate that in this cactus the biosynthetic path over tyramine is predominant.

Of the partially methylated dopamine derivatives 5 and 6 the latter compound,

TABLE I. Incorporation of Radioactive Compounds into Mescaline.

No.	PRECURSOR Name	Formula	% INCORPORATION L. williamsii		T. pachanoi
1	Tyrosine		0.07	0.02	0.59
2	Tyramine		0.07	0.34	3.08
3	DOPA		0.18	0.59	0.71
4	Dopamine		0.67	1.20	5.04
5	4-Methoxy-3-hydroxy--phenethylamine		0.004	0.006	0.41
6	3-Methoxy-4-hydroxy--phenethylamine		1.85	2.75	6.20
7	3,4-Dimethoxy--phenethylamine		0.01	0.14	0.20
8	3,4,5-Trihydroxy--phenethylamine		0.56	0.96	16.3
9	3,5-Dihydroxy-4-methoxy--phenethylamine		0.02	0.01	0.48
10	3,4-Dihydroxy-5-methoxy--phenethylamine		2.04	1.56	31.6
11	3,4-Dimethoxy-5-hydroxy--phenethylamine		0.22	0.11	0.11
12	3,5-Dimethoxy-4-hydroxy--phenethylamine		23.0	20.7	23.4

3-methoxy-4-hydroxyphenethylamine, shows a better incorporation than dopamine into mescaline in both cacti. The isomer 5 is not incorporated in L. williamsii and very little in T. pachanoi. The identification of 6 in T. pachanoi suggests that it is a true precursor of mescaline. Similar incorporations of these compounds into mescaline in L. williamsii have recently been reported by Khanna et.al. (6). These authors also report a very high incorporation (19.43%) of 3,4-dimethoxyphenethylamine 7 into mescaline (7). In our experiments neither in L. williamsii nor in T. pachanoi this amine was incorporated to a significant degree. 3,4-Dimethoxyphenethylamine 7 has been identified by us in both cacti (4) and possibly this compound is a methylation product of 6 that can not be further methabolized to mescaline or to the tetrahydroisoquinoline alkaloids (3,9).

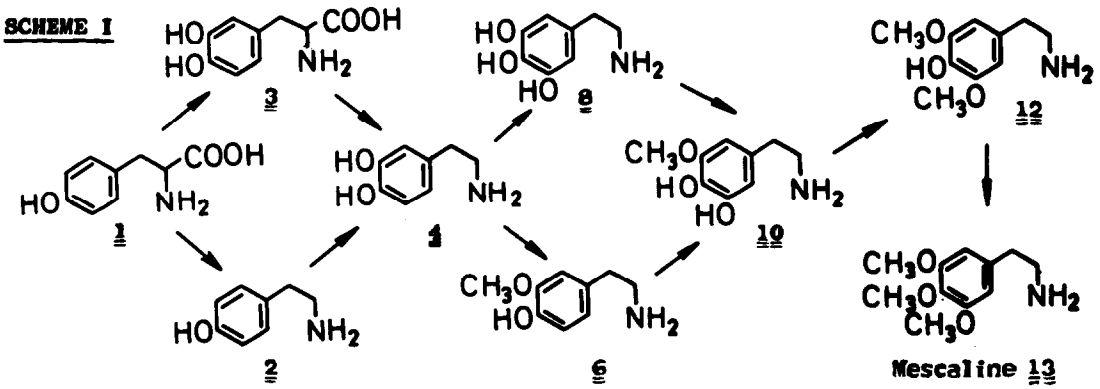
3,4,5-Trihydroxyphenethylamine 8 is incorporated in mescaline in L. williamsii to an extent roughly equal to that of dopamine whereas in T. pachanoi it is very efficiently converted to mescaline. Khanna et.al. (6) report an incorporation of 0.72% of 8, though they regard this incorporation as not very significant.

3,4-Dihydroxy-5-methoxyphenethylamine 10 is efficiently incorporated into mescaline in both cacti and Bennington and Morin have shown (8) that enzymatic oxidation of 3-methoxy-4-hydroxyphenethylamine 6 in fact yielded compound 10. In this oxidation system 3,4-dimethoxyphenethylamine 7 served as a poor substrate (8) and this is fully in line with our findings.

Compounds 9 and 11 are not incorporated into mescaline to a significant degree. The high utilization of 3,5-dimethoxy-4-hydroxyphenethylamine 12 for the synthesis of mescaline in both cacti suggests that this compound is a direct precursor.

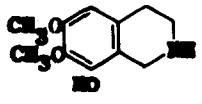
Thus, based on the results of the incorporations in Table I, a biosynthetic route from tyrosine 1 to mescaline 13 as shown in Scheme I is suggested.

SCHEME I



The labelled compounds in Table I were also tested in L. williamsii as precursors of the tetrahydroisoquinoline alkaloid anhalamine 14. The incorporation values for these compounds into mescaline and into anhalamine in the same cactus were very much the same except for compounds 11 and 12. 3,4-Dimethoxy-5-hydroxyphenethylamine 11, found to occur in L. williamsii, was not incorporated into mescaline but it was incorporated into anhalamine 14 better than any other precursor tested (3.03%). In contrast compound 12, an effective progenitor of mescaline, was not incorporated into anhalamine. This is in agreement with our hypothesis that the step determining whether the common precursor will be transformed into mescaline or tetrahydroisoquinoline alkaloids is a methylation of 3,4-dihydroxy-5-methoxyphenethylamine 10 on the meta- or para-hydroxy group.

However, this hypothesis is inconsistent with the finding of Battersby et.al. (9) that compounds 6, 10 and 11 were all incorporated to a lower extent than dopamine 4 into pellotine 15 in L. williamsii and particularly that the incorporation 3,4-dimethoxy-5-hydroxyphenethylamine 11 was only 0.028%. In accordance with Battersby's results we found minute incorporations of the compounds 6, 10 and 11 into anhalonine 16. Further work to establish the pathways to the different tetrahydroisoquinolines in peyote is under progress.



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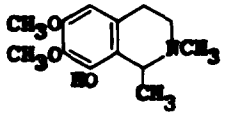

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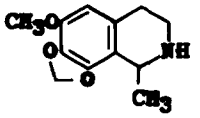

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