Tetrahedron Letters No.42, pp. 4437-4440, 1968. Pergamon Press. Printed in Great Britain.

BIOSYNTHESIS OF MESCALINE AND ANHALAMINE IN PEYOTE. II[a].

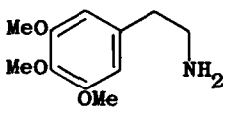
Jan Lundström and Stig Agurell

Department of Pharmacognosy, Royal Pharmaceutical Institute,

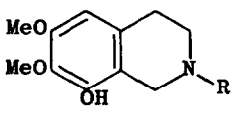
113 86 Stockholm, Sweden.

(Received in UK 24 June 1968; accepted for publication 25 July 1968)

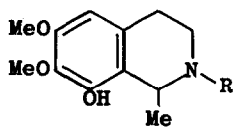
The hallucinogenic alkaloid mescaline (I) occurs together with a number of closely related phenylethylamines and tetrahydroisoquinolines such as anhalamine (II,R=H) in the peyote cactus, Lophophora williamsii (Lem.) Coult. The purpose of a part of our investigations on cactus alkaloids is to determine the biosynthetic sequences leading from tyrosine to mescaline and to the tetrahydroisoquinolines. Previously some information concerning these pathways was obtained by us (1), Leete (2), Battersby et al. (3) and McLaughlin et al. (4). In order to gain further information, we have now tested a number of phenylethylamines substituted with none to three hydroxy- or methoxygroups as precursors of mescaline (I) and anhalamine (II,R=H).



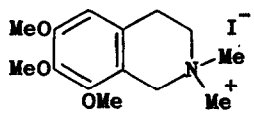
(I)



(II)



(III)



(IV)

The labelled precursors shown in Table 1 were fed to cacti. Radioactive mescaline and anhalamine were isolated and crystallized as hydrochlorides to constant specific activity[b]. Whenever feasible, the position of the label in the molecule was determined by degradation.

The results on the incorporation experiments are reported in Table 1.

---

a) Part I: ref. (1). Supported by the Swedish Natural Science Research Council.

b) Mescaline, anhalamine and anhalonidine were isolated by TLC (1,9) and by gas chromatography (5% SE-30 or 5% XE-60 on Chromosorb W-AQ/DMCS 60/80 mesh, 0.6 x 180 cm column, 185°, Aerograph 202).

TABLE 1

Incorporation of Radioactive Compounds into Mescaline and Anhalamine [a].

PRECURSOR	Amount fed mg	Amount fed μC	MESCALINE Incorp. % [b]	MESCALINE Spec. act. μC/mM x 10^{-2}	ANHALAMINE Incorp. % [b]	ANHALAMINE Spec. act. μC/mM x 10^{-2}
Phenylethylamine-1-^{14}C	0.78	10[c]	<0.005		0.007	1.13
	1.56	20[d]	<0.002		0.002	0.66
Tyramine-1-^{14}C	0.42	10[c]	0.07	8.78[e]		
	0.42	10[d]	0.34	9.60[e]	0.34	26.9[f]
Dopamine-1-^{14}C	0.34	10[c]	0.67	13.3[e]	1.73	149.0[f]
	0.34	10[d]	1.20	18.4[e]		
Dopamine-1-^{14}C	30.1	9.7[c]	0.61	16.0[e]		
	30.1	9.7[d]	1.47	33.9[e]	0.93	72.6[f]
3,4,5-Trihydroxyphenyl-ethylamine-1-^{14}C	16.3	7.5[c]	0.54	6.66[e]		
	16.3	7.5[d]	0.96	10.1[e]	1.73	77.1[f]
4-Methoxyphenylethyl-amine-1-^{14}C	0.38	10[c]	0.01	0.74	0.004	0.48
	0.38	10[d]	0.02	0.57	0.013	1.35
3,4-Dimethoxyphenyl-ethylamine-1-^{14}C	0.38	10[c]	0.01	0.34	0.014	3.45
	0.38	10[d]	0.14	4.02	0.033	3.35
Mescaline-1-^{14}C	0.46	10[d]			0.020	1.01

a) Experimental details are described previously (1,9). Dopamine -1-^{14}C was prepared by demethylation (10) of 3,4-dimethoxyphenylethylamine-1-^{14}C and crystallized as the hydrochloride. 3,4,5-Trihydroxyphenylethylamine-1-^{14}C was similarly prepared from mescaline-1-^{14}C (11). Precursors were, by chromatogram scanning, shown to be over 99.9% pure.

b) "Incorp. %" = mg alkaloid isolated x spec. act. One cactus normally yielding 70-150 mg mescaline and 20-40 mg anhalamine was used in each experiment.

c) Precursor exposed for 10 days.

d) Precursor exposed for 20 days.

e) Degraded to 3,4,5-trimethoxybenzoic acid containing not more than 2.4% of the activity of mescaline.

f) Anhalamine (II,R=H) was converted (2) to O,N-dimethylanhalamine methiodide (IV) (97-98% of the specific activity of anhalamine) which was degraded (5) to 3,4,5-trimethoxyphthalic anhydride (C-3 of anhalamine lost) having not more than 2% of the specific activity of anhalamine.

Our experiments show that phenylethylamine is at best a poor precursor of mescaline and anhalamine. This can be expected from McLaughlin's recent finding (4), that phenylalanine, the corresponding amino acid, is poorly incorporated into mescaline.

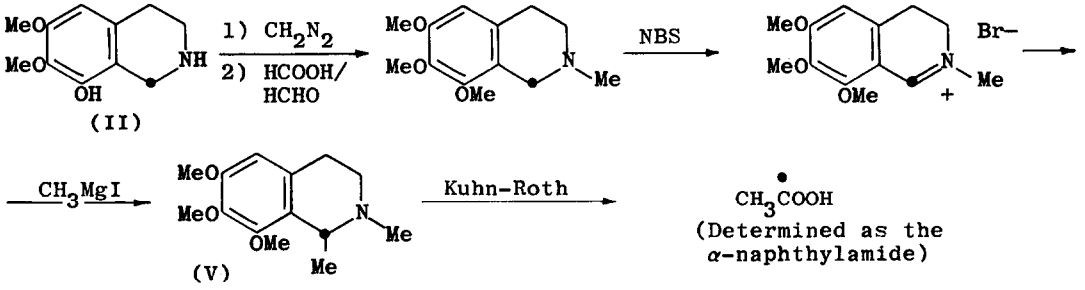
It is also apparent that neither 4-methoxyphenylethylamine nor 3,4-dimethoxyphenylethylamine, the latter compound present in peyote (6), are appreciably incorporated into mescaline or anhalamine. The slight incorporation of mescaline into anhalamine may be explained by a previous partial demethylation, but on the whole it would appear that mescaline is not a significant precursor of the tetrahydroisoquinoline alkaloids of peyote. Instead, the tetrahydroisoquinolines and mescaline are formed by different routes from a common precursor.

In contrast, compounds containing one, two or three hydroxyl groups are all efficient progenitors of both mescaline and anhalamine. Particularly interesting is the fact that 3,4,5-trihydroxyphenylethylamine is utilized as effectively as dopamine. Of these phenolic compounds, tyramine is known to occur in peyote (4) while dopamine has been found in other cacti, e.g. Carnegia gigantea (7). 3,4,5-Trihydroxyphenylethylamine has so far not been encountered in nature.

In conclusion, these results would tend to support (4,8) a sequence of hydroxylations from tyrosine via tyramine and dopamine and from tyrosine via DOPA and dopamine, leading to a tri-substituted phenolic phenylethylamine. It is possible that this latter compound may be 3,4,5-trihydroxyphenylethylamine itself, which is well incorporated into the ring closed tetrahydroisoquinolines as well as into mescaline, or it may be a methylated derivative thereof. In this connection, it may be pertinent to mention that a dimethoxyhydroxyphenylethylamine has been identified by gas chromatography - mass spectrometry in the mescaline producing cactus Trichocereus pachanoi. If this compound is 3,4-dimethoxy-5-hydroxyphenylethylamine, on paper an intriguing common precursor still has to be determined (6). In any case, our data suggests that at least one phenolic group is necessary for an efficient metabolism of a precursor to mescaline or anhalamine.

Theoretically, an appropriate phenylethylamine combined with a one carbon unit could produce the anhalamine structure (II,R=H). A further addition of a one carbon unit provides the anhalonidine (III,R=H) system. (^{14}C-methyl)-Methionine fed to the cactus afforded radioactive anhalamine (0.18%, 0.44% incorporation, two experiments) and anhalonidine (0.09%, 0.95% incorporation). In anhalonidine, all activity (96% and 100%) was located in the O-methyl groups (Zeisel). This is in agreement with Battersby's finding (3) that the two carbon unit of pellotine (III,R=CH_3) is not derived from the methyl group of methionine. It has been shown earlier that the O-methyl groups of mescaline and pellotine are derived from methionine (1,3).

The O-methyl groups of anhalamine carried 53% and 65% of the total activity. Anhalamine (II) was further degraded as shown below to yield from the Kuhn-Roth oxidation of (V) acetic acid containing 42% and 25% of the radioactivity. Thus, the bridge carbon of anhalamine is derived from the methyl group of methionine, but whether or not the biosynthetic process includes an oxidative cyclization of an N-methylated derivative of phenylethylamine still has to be proven.



REFERENCES

1. S. Agurell, J. Lundström and F. Sandberg, Tetrahedron Letters 2433 (1967).
2. E. Leete, J. Am. Chem. Soc. 88, 4218 (1966).
3. A. R. Battersby, R. Binks and R. Huxtable, Tetrahedron Letters 563 (1967).
4. J. L. McLaughlin and A. G. Paul, Lloydia 30, 91, 100 (1967).
5. E. Späth and F. Beche, Ber. 67, 2400 (1934).
6. S. Agurell and J. Lundström, J. Chromatog. in press and to be published.
7. C. Steelink, M. Yeung and R. L. Caldwell, Phytochemistry 6, 1435 (1967).
8. L. Reti in Fortsch. Chem. Organ. Naturstoffe 6, 268 (1950).
9. J. Lundström and S. Agurell, J. Chromatog. 30, 271 (1967).
10. A. R. Battersby and A. J. Frances, J. Chem. Soc. 4078 (1964).
11. G. Hahn and F. Rumpf, Ber. 71, 2141 (1938).