

Biosynthesis of Mescaline

By K. L. KHANNA, H. ROSENBERG, and A. G. PAUL*

(College of Pharmacy, The University of Michigan, Ann Arbor, Michigan 48104)

Summary A pathway of biosynthesis of mescaline from 3,4-dihydroxyphenethylamine via *m*-*O*-methylation is proposed.

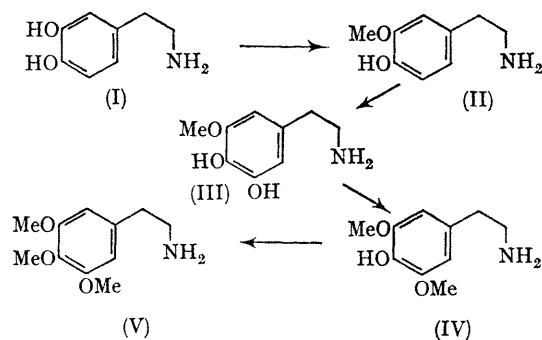
RECENT proposals^{1,2} that methoxylated phenolic intermediates may be involved in the biosynthesis of mescaline (V) have, in part, been substantiated by us. Tracer experiments of *Lophophora williamsii* with [8-¹⁴C]labelled 4-hydroxy-3-methoxy- (II), 3-hydroxy-4-methoxy-, and 5-hydroxy-3,4-dimethoxy-phenethylamine were carried out in the manner previously described.^{3,4} The mescaline isolated in each instance was assayed for radioactivity and then degraded in order to determine specific incorporation. The results showed that 4-hydroxy-3-methoxyphenethylamine was incorporated to a significant extent (1.45%) with >99% of the radioactivity residing in the 8 position of mescaline. However, only 0.10% of the radioactivity of 3-hydroxy-4-methoxyphenethylamine and 0.21% of the radioactivity of 5-hydroxy-3,4-dimethoxyphenethylamine were recovered as mescaline. Contrary to the finding of Lundström and Agurell,⁵ we have not found 3,4,5-trihydroxyphenethylamine to be an efficient precursor (0.72% incorporation).²

The low percentage of incorporation of 5-hydroxy-3,4-dimethoxyphenethylamine would indicate that this compound is not a significant intermediate in the biosynthesis pathway of mescaline as suggested by Agurell and Lundström.¹ It appears that in *L. williamsii*, the pathway of biosynthesis involves *m*-*O*-methylation of 3,4-dihydroxyphenethylamine (I) rather than *p*-*O*-methylation as an

initial step. The earlier sequences in the pathway from phenylalanine to 3,4-dihydroxyphenethylamine have been reported.^{3,4}

These data and the reported occurrence of 4-hydroxy-3,5-dimethoxyphenethylamine (IV) in the mescaline-producing cactus *Trichocereus pachanoi*^{1,6} support the hypothesis that mescaline is formed from 3,4-dihydroxyphenethylamine by the pathway shown. Whether 5-hydroxy-3,4-dimethoxyphenethylamine serves as a precursor of the phenolic tetrahydroisoquinoline alkaloids in *L. williamsii* is under investigation.

This investigation was supported by a research grant from the National Institute of Mental Health, U.S. Public Health Service, Bethesda, Maryland.



(Received, January 22nd, 1969; Com. 093.)

¹ S. Agurell and J. Lundström, *Chem. Comm.*, 1968, 1638.

² A. G. Paul, H. Rosenberg, and K. L. Khanna, *Lloydia*, 1969, 32, in the press.

³ J. L. McLaughlin and A. G. Paul, *Lloydia*, 1967, 30, 91.

⁴ H. Rosenberg, J. L. McLaughlin, and A. G. Paul, *Lloydia*, 1967, 30, 100.

⁵ J. Lundström and S. Agurell, *Tetrahedron Letters*, 1968, 4437.

⁶ S. Agurell, *Lloydia*, in the press.