Apparent Intermediates in the Biosynthesis of Mescaline and Related Tetrahydroisoquinolines†

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WE have investigated the alkaloid fractions of *Lophophora williamsii* and *Trichocereus pachanoi* by means of g.l.c. and g.l.c.–mass spectrometry‡ and have detected 4-hydroxy-3-methoxyphenethylamine (II), 5-hydroxy-3,4-dimethoxyphenethylamine (VI), and 4-hydroxy-3,5-dimethoxyphenethylamine (IV) as possible intermediates on the bio-synthetic pathway from tyrosine to mescaline (V) and the tetrahydroisoquinolines.

Previous work[1,2] on the biosynthesis of mescaline (V) and tetrahydroisoquinolines (VII) in peyote (*L. williamsii*) show that 4-methoxy- and 3,4-dimethoxy-phenethylamine are not significant precursors whereas tyramine, dopamine, and

† The present paper constitutes part of the series "Detection of Alkaloid Intermediates by Gas Chromatography–Mass Spectrometry".

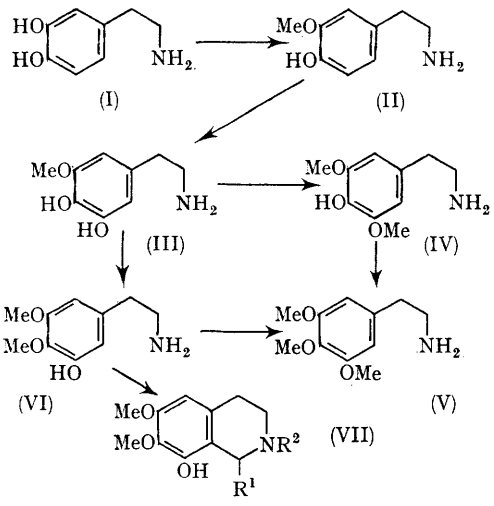
‡ Gas chromatography was carried out on columns of 5% SE-30 on GasChromP or 5% XE-60 on Chromosorb W. For gas chromatography–mass spectrometry an LKB 9000 was used (J. Lundström and S. Agurell, *J. Chromatog.* **1968, 36, 105**). Retention times and mass spectra, identical with those of synthetic reference material (ref. 3; J. M. Bobbitt and T. T. Chou, *J. Org. Chem.*, **1959, 24, 1106**) were used to establish the identity of each compound.

3,4,5-trihydroxyphenethylamine (all phenols), are well incorporated. By analogy with animal metabolism of similar compounds[3,4] one could expect a biosynthetic pathway from dopamine I to mescaline and tetrahydroisoquinolines involving methoxylated phenolic intermediates. Such potential precursors carrying both methoxy- and hydroxy-groups have not previously been found in plants.

We also wished to explain the fact that the peyote cactus produces both mescaline and a number of tetrahydroisoquinolines, *e.g.* anhalamine (VII; $R^1 = R^2 = H$), whereas *T. pachanoi*[5] contains only mescaline.

In *T. pachanoi*, substantial amounts of 4-hydroxy-3-methoxyphenethylamine (II) were found, together with traces of 4-hydroxy-3,5-dimethoxyphenethylamine (IV). Peyote was found to contain an isomer of the latter, 5-hydroxy-3,4-dimethoxyphenethylamine (VI). These three compounds, not previously reported in plants, fit well into the biosynthetic scheme shown in the Figure. The first step is the *m-O*-methylation of dopamine to (II) followed by a hydroxylation to (III). Subsequent methylation of the latter on the *p*-hydroxy-group yields (VI) which can easily undergo ring-closure to the tetrahydroisoquinolines (VII) by a Mannich-type reaction, or further methylation to form mescaline (V). If (III) is methylated in the *meta*-position instead, the resulting compound (IV) would have no activated site suitable for ring-closure and consequently would tend to yield only mescaline (V).

Hence, the basic difference between *T. pachanoi* and *L. williamsii*, may be due to *m-O*-methylation of a precursor in the former and *p-O*-methylation in the latter. This hypothesis is now being tested with radioactive precursors.



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