

## THE SEPARATE ROLES OF HYGRINE ENANTIOMERS IN THE BIOSYNTHESIS OF TROPANE ALKALOIDS

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It is well established that the pyrrolidine part of the bicyclic tropane ring system is derived in nature from ornithine which incorporates in a non-symmetrical manner (Leete, 1962). Transamination of the  $\alpha$ -amino group of ornithine followed by decarboxylation eventually produces a reactive N-methyl- $\Delta^1$ -pyrrolinium cation (Leete and Nelson, 1969). Acetoacetate which supplies the remaining three carbons of the tropane ring attacks the  $\alpha$ -imino carbon of the  $\Delta^1$ -pyrrolinium cation producing hygrine. Hygrine has an asymmetric centre [C(2)] and the absolute stereochemistry of the enantiomers has been deduced (Lukeš and others, 1960), (+) & (-)-hygrines have the D and L configuration respectively.

Hygrine-[2'- $^{14}$ C] was synthesized by reducing N-methyl-2-pyrrolidone with lithium aluminium hydride and condensing the product with ethyl acetoacetate-[3- $^{14}$ C] in aqueous solution at pH 7 for 40 hours (Galinovsky and others 1951; O'Donovan and Keogh, 1969). The hygrine was resolved as the D(+)-tartrate and the separate enantiomers were fed via the roots to five-month-old Datura innoxia plants. Because the optical isomers easily racemise the bases were administered as the tartrates. After seven days the root alkaloids 3 $\alpha$ ,6 $\beta$ -ditigloyloxytropane, 3 $\alpha$ ,6 $\beta$ -ditigloyloxytropan-7 $\beta$ -ol, hyoscyne, hyoscyamine and cuscohygrine were isolated from both groups of plants without dilution and their specific activities were determined. D(+)-Hygrine serves as a precursor for the tropane alkaloids but cuscohygrine is formed from both optical isomers. Thus, in the formation of the tropane ring in Datura C(1) is the first attachment point with acetoacetate, C(5) the second. Cuscohygrine has two asymmetric centres and in nature it exists as the optically inactive meso form and it is perhaps not surprising that either optical isomer of hygrine may serve as a precursor. The labelled hyoscyamine was hydrolysed by boiling with barium hydroxide solution and the resultant tropine was oxidized to tropinone with chromium trioxide in acetic acid. The tropinone was then coupled with phenyl magnesium bromide to yield 3-phenyltropan-3-ol. The latter compound when refluxed with aqueous permanganate gave benzoic acid which contained all the radioactivity of the original hyoscyamine [C(3) of the tropane ring] thus confirming the non-random incorporation of hygrine.

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