

## THE BIOSYNTHESIS OF HYGRINE AND TROPANE ALKALOIDS

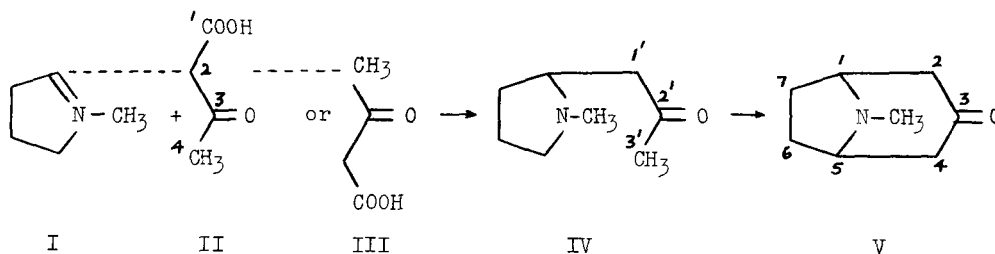
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It has been shown that the pyrrolidine part of the tropane ring system is formed in nature from an ornithine derived  $N$ -methyl- $\Delta^1$ -pyrrolinium cation I (Leete and Nelson 1969). The remaining carbons C(2) (3) and (4) are known to be of acetate origin (Kaczkowski and others 1960 and 1961). We have recently demonstrated that D(+)-hygrine IV is efficiently metabolised into several tropane alkaloids V including hyoscyne and hyoscyamine in *Datura* (McGaw and Woolley 1977). Apart from the earlier work by O'Donovan and Keogh (1969) who demonstrated that ornithine and acetate were involved in the biosynthesis of hygrine, no further work on this alkaloid has been reported.

Hygrine is the chief alkaloid of *Nicandra physaloides* (Romeike 1965) and for this investigation sodium acetoacetate- $[3-^{14}C]$  prepared by mild hydrolysis of the ethyl ester was fed to 10 three-month-old plants via cotton wicks sewn into the stems. After 2 weeks the plants were harvested and the alkaloids were separated by partition column chromatography on kieselguhr at pH 6.8 (Evans and Partridge 1952). Hygrine was eluted from the column with chloroform (after tropinone) and it was found that the sodium acetoacetate- $[3-^{14}C]$  incorporated into the C(2') position of the side-chain.

From a mechanistic point of view, it is likely that the reactive methylene, C(2) of acetoacetate II, reacts with  $N$ -methyl- $\Delta^1$ -pyrroline. However, the terminal methyl of the acetoacetate must at some stage be activated to couple with the  $N$ -methylpyrrolidine moiety to give the tropane ring V. It is possible therefore that the terminal methyl of acetoacetate III first couples with  $N$ -methyl- $\Delta^1$ -pyrroline to give hygrine.

Which of the two alternative couplings is used *in vivo* to produce hygrine may be solved by feeding sodium acetoacetate- $[4-^{14}C]$  to *Nicandra* plants. The label will be expected at either C(1') or C(3') of the side-chain of hygrine after it has been degraded.



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