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BIOSYNTHESIS OF DIHYDROERGOT ALKALOIDS

By Kevin D. Barrow*+, Peter G. Mantle and Francoise R. Quigley.

(Biochemistry Department, Imperial College of Science and Technology, South Kensington, London S.W.7)

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The biosynthesis of polypeptide ergot alkaloids (Ia) involves the intermediate lysergic acid (Ib).[1] The role of 6-methylergol-8-ene-8-carboxylic acid (II)[2] is less clear and the migration of the double bond from the 8,9 to the 9,10 position is also poorly understood.[3]

Some years ago one of us isolated dihydroergosine (III) from cultures of the fungus *Sphacelic sorghi*.[4] This is the only naturally occurring polypeptide dihydroergot alkaloid known so far although dihydroclavine alkaloids are more widely distributed and have been isolated from numerous microorganisms.[5] These dihydroclavine alkaloids are considered to be formed by reduction of the corresponding clavine alkaloids.[6] Possible pathways to dihydroergosine could be analogy involve reduction of the 9,10 double bond of ergosine or a precursor of ergosine or involve the reduction of an alkaloid containing an 8,9 double bond. It is known that the clavine alkaloids incorporate the 5-pro-R hydrogen from mevalonic acid and that this hydrogen is located at position 10 in the ergoline ring system.[7] The 5-pro-S hydrogen is lost in the cyclisation of ring C.

+ Present address: School of Biochemistry,
University of New South Wales,
P.O. Box 1,
Kensington. N.S.W. 2033
Australia.

We therefore fed [5(R,S)-^{3}H, 2-^{14}C] mevalonate ($^{3}H/^{14}C$, 11.4/1; atomic ratio 2:1) to cultures of *S. sorghi* and isolated dihydroergosine which showed 1.1% incorporation of ^{14}C and $^{3}H/^{14}C$, 5.5/1; atomic ratio 1:1. This clearly shows that one hydrogen from the 5-position of mevalonic acid is present in dihydroergosine and this rules out any biosynthetic pathways involving 9,10 unsaturated alkaloids.

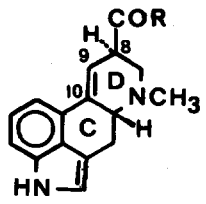
We then turned our attention to the minor alkaloids of *S. sorghi* and isolated and characterized festuclavine (IVa), dihydroelymoclavine (IVb) and chanoclavine I (V). As well we detected traces of other unidentified oxygenated clavine and polypeptide alkaloids. The only amphoteric tryptophan metabolite we could isolate was dihydrolysergic acid (IVc).

The results of our feeding experiments are shown in the table.

TABLE. Incorporation of radioactive precursors into dihydroergosine in *S. sorghi*

Compound fed	% incorporation
Mevalonic acid	1.1%
Tryptophan	11
Agroclavine (VI)	1.8
Festuclavine (IVa)	31
Dihydroelymoclavine (IVb)	33
Dihydrolysergic acid (IVc)	32

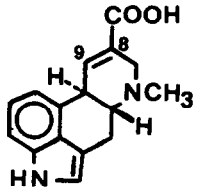
These results show that dihydroclavine alkaloids are very efficient precursors of dihydroergosine and suggest a possible pathway:



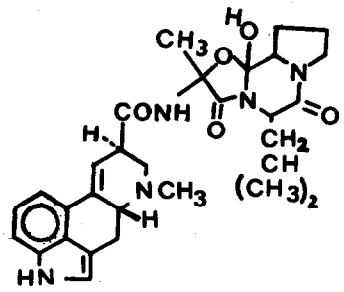
I

(a) R= NHR'

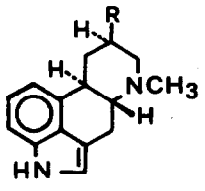
(b) R= OH



II



III

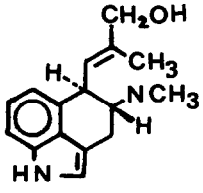


IV

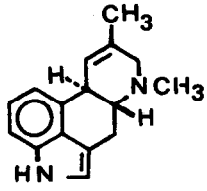
(a) R=CH_3

(b) R=CH_2OH

(c) R=COOH



V



VI

festuclavine → dihydroelymoclavine → dihydrolysergic acid → dihydroergosine

Thus, in contrast to normal ergot alkaloid biosynthesis the methyl group hydroxylated and oxidized to a carboxyl group is not activated by a double bond. The role of agroclavine is less clear as the incorporation was markedly lower than the dihydroalkaloids and we were unable to detect any agroclavine as a metabolite of *S. sorghi*. We were also unable to detect the presence of any dihydrochanoclavines which have been converted into dihydroclavine and other alkaloids by *Claviceps purpurea*.[8] Agroclavine could be an obligatory but transient intermediate and undergo immediate reduction to festuclavine and so never accumulate.

In feeding experiments involving festuclavine considerable activity (up to 45% in short term experiments) was always found in dihydroelymoclavine. The same facile hydroxylation of festuclavine probably also operates in *Claviceps gigantea* where the major metabolite is dihydroelymoclavine and elymoclavine does not appear to be an intermediate.[9]

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