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The Role of the Chanoclavines in the Biosynthesis of Ergot Alkaloids

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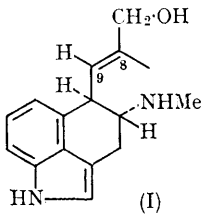
WHEREAS it is well established that the tetracyclic clavines and the lysergic acid part of ergot alkaloids are biosynthesised from mevalonic acid and tryptophan, little is known about the intermediates in this process.[1] In particular different roles have been assigned to chanoclavine-I (I)[2] at a time when neither its detailed stereochemistry nor the existence of stereoisomers thereof[3] were known. The available experimental data have not so far contributed to a clarification of the picture.[1] Chemical evidence for the stereochemistry previously assigned[3] to chanoclavine-I (I) and isochanoclavine-I (II) has been presented in the preceding Communication.[4] We now report on the course of the biosynthesis of the chanoclavines and their role in the formation of tetracyclic clavines.

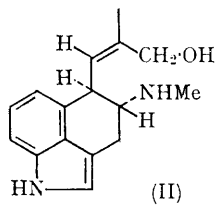
Rigorous purification of the alkaloidal mixture isolated upon feeding (10 days) of sodium DL-[2-^{14}C]mevalonate to surface cultures of a *Claviceps* strain from *Pennisetum typhoideum* Rich.[2] (total incorporation *ca.* 10%) yielded large amounts of labelled agroclavine (IV) (5·5% incorporation) and elymoclavine (V) (3·5% incorporation) as well as small radioactive samples of the three chanoclavines (I), (II), and (III) (0·01%, 0·02%, 0·025% respective incorporation).

Degradation of the labelled (IV) and (V) by standard procedures[5] showed that in both cases C-17 carries >90% and C-7 *ca.* 7% of the total activity, in good accord with previous investigations.[5] On the other hand, similar degradations of the chanoclavines (I), (II), and (III) indicated that in all of them, and irrespective of the geometry of the 8,9-double bond, >90% of the activity was located at the *C*-methyl group and *ca.* 7% at the hydroxymethyl group. Therefore chanoclavine-I (I) has an unexpected[6] *trans*-relationship of the labelled atom and the olefinic proton. From the observed label distribution as well as from the known stereochemistry it is tempting to conclude that only isochanoclavine-I (II) fulfills the requirements for a precursor of the tetracyclic clavines. This, however, is not the case, as indicated by further experimentation.

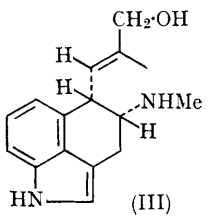
Biosynthetically labelled elymoclavine (V) from the above experiment was converted by the procedure outlined in the preceding Communication[4] to a sample of (I) with >90% of the label confined to the hydroxymethyl group. Upon administration of this material to submerged cultures of *Claviceps paspali* Stevens *et* Hall,[7] a 2% incorporation into 6-methyl-8(9)-ergolen-8-carboxylic acid (VI) was observed. Similarly, feeding of the same precursor to surface cultures of our *Pennisetum* strain gave, *inter alia*, radioactive (IV) (7%, 10%, 9% respective incorporation in three separate experiments), shown by standard degradations to



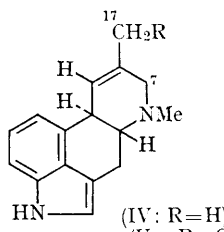
(I)



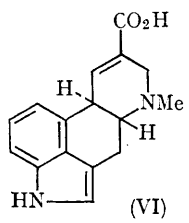
(II)



(III)



(IV: R=H)
(V: R=OH)



(VI)

carry 96·4% of the activity at C-7 and 6·4% at C-17. Thus, conversion of (I) into (IV) is accompanied at some stage by a *trans–cis* isomerisation of the double bond. Nevertheless, repeated experiments carried out under similar conditions with CH_2·OH-labelled (II), prepared by the u.v.-isomerisation, previously described,[4] of labelled (I), failed to reveal any significant incorporation into the alkaloids of both the *Pennisetum* and *Paspali* strain.

Although it does not follow from our results that (I) is an obligatory intermediate, it now seems worthwhile to consider whether the apparently "normal"[6] specific incorporation of radioactivity

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from [2-^{14}C]mevalonate into C-17 of the tetracyclic ergot alkaloids[1,5] may actually *not* fall into the normal scheme of terpene biosynthesis but rather represents the fortuitous outcome of a more complex sequence of transformations.

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[1] For general reviews *cf.* F. Weygand and H.-G. Floss, *Angew. Chem. Internat. Edn.*, 1963, **2**, 243; S. Agurell, *Acta Pharm. Suecica*, 1966, **3**, 71.
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[4] W. Acklin, T. Fehr, and D. Arigoni, *Chem. Comm.*, 1966, preceding Communication.
[5] S. Bhattacharji, A. J. Birch, A. Brack, A. Hofmann, H. Kobel, D. C. C. Smith, H. Smith, and J. Winter, *J. Chem. Soc.*, 1962, 421.
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