Chemical Communications

NUMBER 3/1967 8 FEBRUARY

Chanoclavines and the Biosynthesis of Ergot Alkaloids

By H. G. Floss*, U. Hornemann*, and N. Schilling
(*Organisch-Chemisches Institut der TH München, Germany*)
D. Gröger and D. Erge
[*Institut für Biochemie der Pflanzen der DAW, Halle (Saale), Germany*]

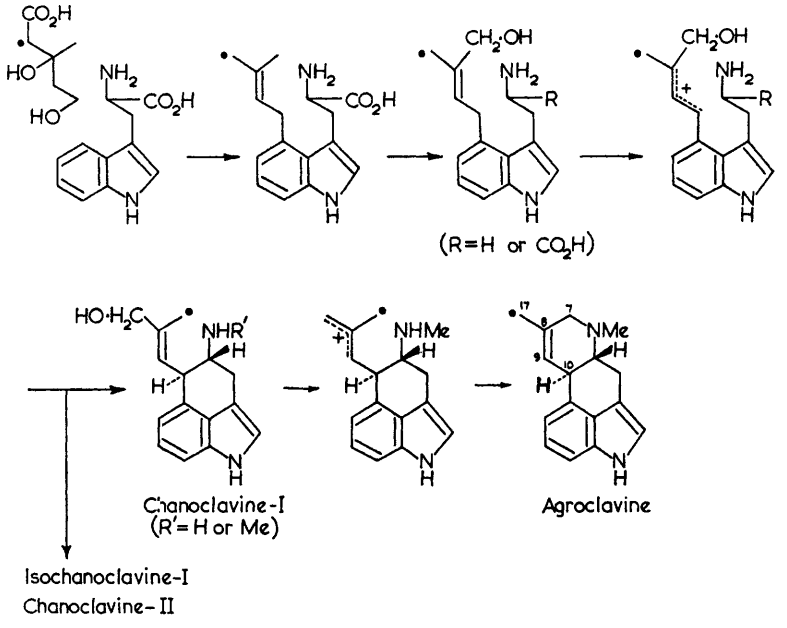
Although the biological origin of ergot alkaloids from tryptophan and mevalonic acid has been well established, the detailed mechanism of this biosynthetic pathway still remains obscure.[1] We have recently shown[2] that chanoclavine-I, one of three chanoclavine isomers isolated from Claviceps,[3] is an efficient precursor of the tetracyclic ergolines, agroclavine, elymoclavine, and lysergic acid amide. The results suggested that the cyclization of chanoclavine-I involves an isomerization at the exocyclic double bond. This has now been firmly established by further experiments. In agreement with results of Arigoni and co-workers,[4] [2-^{14}C]-mevalonic acid on feeding to a *Claviceps paspali* strain[2] gave chanoclavine-I, which by Kuhn–Roth oxidation was shown to carry 92% of its label in the *C*-methyl group. This material when fed to Claviceps strain SD 58 gave [^{14}C]elymoclavine, which was degraded by Emde–Birch fission[5] and subsequent Kuhn–Roth oxidation to give acetic acid (C-7 + C-8) containing 12% of the label. Consequently, C-17 of elymoclavine must carry 88% of the label and is thus derived from the *C*-methyl group of chanoclavine-I.

In order to gain more information about the mechanism of this isomerization, chanoclavine-I carrying tritium at C-9 and C-10† respectively plus a ^{14}C reference label was prepared biosynthetically from corresponding mevalonic acids. Conversion of these samples into elymoclavine by strain SD 58 occurred with 100% retention of tritium at C-10 and with 92% retention of tritium at C-9. Thus, neither of the two hydrogens is lost during the isomerization. The slight decrease in the T/^{14}C ratio observed with tritium at C-9 is attributed to an isotope effect in a yet unknown reaction not involved in the isomerization. These results rule out a number of mechanisms which involve isomerization of chanoclavine-I to isochanoclavine-I prior to cyclization.

This was further substantiated by comparing the rates of conversion of agroclavine, chanoclavine-I, isochanoclavine-I, and chanoclavine-II (all labelled biosynthetically with tritium in the indole moiety) into elymoclavine. In replacement cultures of strain SD 58 specific incorporations of 9·6%, 9·0%, 1·9%, and 0·6%, respectively, were observed with these compounds. As a consequence, of the three chanoclavine isomers only chanoclavine-I is a good precursor of tetracyclic ergolines, whereas isochanoclavine-I cannot be regarded as an intermediate in the biosynthesis, although from its stereochemistry (hydroxymethyl group *cis* to ring) it seemed to be the most promising candidate. The same conclusion has independently been reached by Arigoni and co-workers.[4]

* New address: Department of Medicinal Chemistry, School of Pharmacy and Pharmacal Sciences, Purdue University, Lafayette, Indiana, U.S.A.

† Numbering analogous to that of ergolines.



(• Denotes majority of label from [2-^{14}C]mevalonate).

The presently available results are in agreement with, but do not prove, chanoclavine-I as an obligatory intermediate in ergot alkaloid biosynthesis. However, in view of the high incorporation (up to 40%) observed in the conversion of chanoclavine-I into elymoclavine,[2] it seems unlikely that this reaction is only of minor importance in the fungus. Taking into account the observation of Arigoni *et al.*[6] that desoxychanoclavine-I and its *N*-demethylation product are not incorporated into elymoclavine, and providing that chanoclavine-I is an intermediate, the sequence outlined below, involving two isomerizations, can be considered as one possible mechanism of ergot alkaloid formation. As another possibility, the isopentenyl pyrophosphate isomerase reaction in Claviceps might take an unusual steric course.

(*Received, November 22nd*, 1966; *Com.* 921.)

[1] For Reviews see: (a) F. Weygand and H. G. Floss, *Angew. Chem. Internat. Edn.*, 1963, **2**, 243; (b) S. Agurell, *Acta Pharm. Suecica*, 1966, **3**, 71.

[2] D. Gröger, D. Erge, and H. G. Floss, *Z. Naturforsch.*, 1966, **21b**, 827.

[3] D. Stauffacher and H. Tscherter, *Helv. Chim. Acta*, 1964, **47**, 2186.

[4] D. Arigoni and W. Acklin, private communication; W. Acklin, T. Fehr, and D. Arigoni, *Chem. Comm.*, 1966, 799; T. Fehr, W. Acklin, and D. Arigoni, *ibid.*, p. 801.

[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.

[6] T. Fehr, W. Acklin, and D. Arigoni, unpublished results 1965, private communication; D. Arigoni, "Some aspects of mevalonoid biosynthesis". Symposium on Organic Chemical Approaches to Biosynthesis, London, 1965, quoted in ref. 1b.