Biosynthesis of Ergot Alkaloids: Stereochemistry of Hydrogen Elimination From C-4 of Mevalonate

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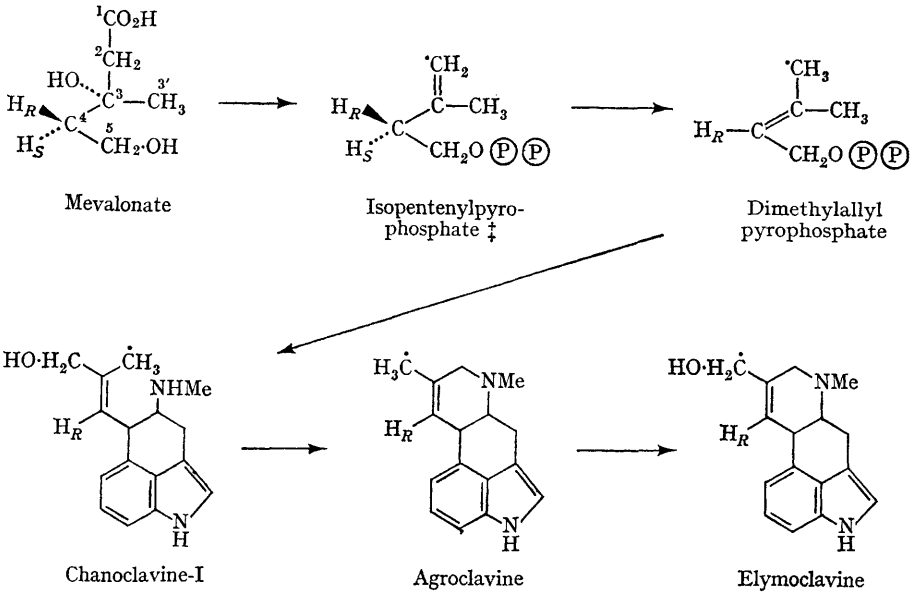
INDIRECT evidence indicates that in the isopentenyl pyrophosphate isomerase reaction the carbon atom originating from C-2 of mevalonate becomes the *trans*-methyl group of dimethylallyl pyrophosphate.† Work with mevalonic acids labelled stereospecifically at C-4 showed that the *S*-hydrogen

† *cis* and *trans* refer to the position relative to the carbon substituent.



‡ The indices *S* and *R* refer to the configuration of the hydrogens in the original mevalonate as defined by Popjak and Cornforth (see ref. 1).

is eliminated in this reaction. The same hydrogen is also eliminated in the condensations of isoprene units which lead to the formation of *trans*-double bonds. However, in the biosynthesis of rubber the *R*-hydrogen is eliminated, resulting in the formation of *cis*-double bonds.[1]

The biosynthesis of ergot alkaloids most likely involves reaction of dimethylallyl pyrophosphate with the 4-position of tryptophan as the initial step.[2] Recently, it has been shown[3,4] that in chanoclavine-I, a precursor of the tetracyclic alkaloids, the label from C-2 of mevalonate is found in the methyl group which occupies the *cis* position at the double bond. Upon subsequent cyclization to give agroclavine this carbon becomes *trans*-oriented. This finding raises the question as to whether the isomerization of isopentenyl pyrophosphate involved in ergot alkaloid formation follows the same steric course as that in the other biological systems so far investigated.

The 4*R*- and 4*S*-isomers (±)-[2-^{14}C,4-^{3}H]-mevalonic acid (Radiochemical Centre, Amersham, 4·5 μcC^{14}, $^{3}H/^{14}C$ = 3·94 and 5 μc ^{14}C, $^{3}H/^{14}C$ = 4·42) were each fed to two 100 ml. shake cultures of *Claviceps* strain SD 58 (5). After six days the cultures were harvested and found to contain 98 mg. and 133 mg. of alkaloid, respectively. Elymoclavine was isolated and crystallized to constant specific activity. ^{14}C-Incorporations were 9·9% and 10·0% and the $^{3}H/^{14}C$ ratios were 2·96 and 0·12, respectively. This corresponds to 70% retention of the *R*-hydrogen and only 3% retention of the *S*-hydrogen. Clearly, the 4*S*-hydrogen of mevalonate is eliminated in the reaction. The somewhat low retention of 4*R*-hydrogen confirms earlier observations with mevalonic acid labelled non-stereospecifically at C-4, and is ascribed to an isotope effect in a subsequent reaction.

The results show that the steric course of the isopentenyl pyrophosphate isomerase reaction involved in ergot alkaloid formation is "normal" with respect to the hydrogen elimination. It seems likely therefore that the overall stereochemistry of the reaction is also "normal", *i.e.*, the label from C-2 of mevalonate should be located in the *trans*-methyl group of the original dimethylallyl residue. As a consequence, two isomerizations at the allylic double bond seem to take place in the formation of ergot alkaloids.

This work was supported by a grant from Eli Lilly and Company.

(*Received, June 6th*, 1967; *Com.* 574.)

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[5] H. G. Floss and D. Groeger, *Z. Naturforsch.*, 1963, **18b**, 519.