

PARTIAL SYNTHESIS OF FESTUCLAVINE*

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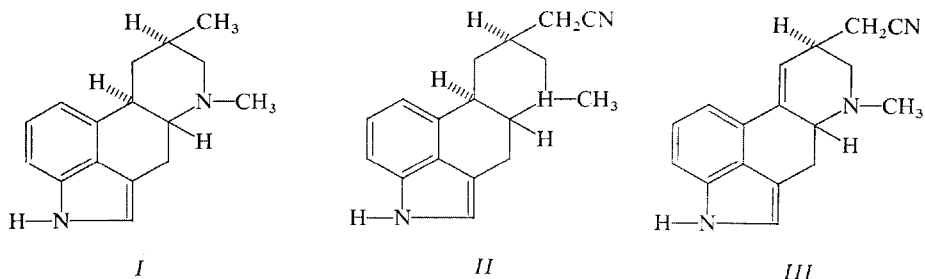
Festuclavine, D-6,8-dimethylergolin-I, was prepared by reductive decyanization of D-6-methyl-8-cyanomethylergolin-I and of the same derivative of $\Delta^{9,10}$ -ergolene with potassium in phosphoric hexamethyltriamide. In the case of the ergolene derivative, the double bond at position 9,10 was also hydrogenated.

Festuclavine, D-6,8-dimethylergolin-I (*I*), was isolated from ergot parasitizing on grasses of genera *Agropyrum* and *Phalaris*¹, from a culture of *Claviceps gigantea*² and from *Aspergillus fumigatus* FRES.^{3,4} In a partial synthesis it was obtained by reduction of agroclavine⁵⁻⁷. Both procedures are rather laborious, the reduction of agroclavine proceeds nonspecifically with the formation of a number of isomeric products.

In the present communication we describe a simple preparation of *I* from the readily available D-6-methyl-8-cyanomethylergolin-I (*II*) (ref.⁸), by a reductive decyanization with potassium in phosphoric hexamethyltriamide. Compound *I* was obtained in the same way from D-6-methyl-8-cyanomethylergolene⁹ (*III*) when, together with the splitting of the nitrile group, the double bond in position 9, 10 was hydrogenated. The yield of *I* was almost quantitative in both cases.

Reductive decyanization of nitriles to hydrocarbons proceeds usually in systems in which the reaction of an alkaline metal with the solvent gives rise to the so-called "solvated" electrons. For a number of aliphatic and aromatic nitriles the most selective system was found to be potassium with hexamethyltriamide of phosphoric acid¹⁰. In other systems, the reductive cleavage of the nitrile group is associated more or less (depending on the structure of the starting nitrile) with the simultaneous reduction of the nitrile group to a primary amine. In the case of aromatic nitriles, application of the system potassium with hexamethyltriamide of phosphoric acid resulted in a partial hydrogenation of double bonds in the aromatic ring¹⁰. In the case of reductive decyanization of *II* and *III* by this system this partial reduction of unsaturated rings A and B of the ergolin skeleton was not observed.

* Part XLV in the series Ergot Alkaloids; Part XLIV: This Journal 41, 1042 (1976).



On the basis of literature data^{11,12} the decyanization is assumed to proceed by a radical-ion mechanism, involving the formation of a complex product with the methylene anion which undergoes solvolysis by water or a protic solvent and breaks down to festuclavine (*I*), potassium hydroxide and potassium cyanide. In the case of the ergolene derivative *III* the reaction is accompanied by a reduction of the double bond in position 9,10 probably by the mechanism shown for the reduction of the isolated carbon double bond by this system¹³. The reduction proceeds highly stereospecifically; the isomeric D-6,8-dimethylergolin-II (costaclavine) was not detected in the reaction mixture. Cleavage of the nitrile group as a whole was demonstrated by titration of potassium cyanide in the mother liquor after separation of *I*; the amount estimated corresponded stoichiometrically to the isolated product.

Biological evaluation of festuclavine (inhibition of secretion of hypophyseal prolactin in rats and others) will be described elsewhere.

EXPERIMENTAL

The melting point was determined in Kofler's block and is not corrected. The sample for elementary analysis was dried at 100°C and 0.5 Torr to constant weight.

D-6,8-Dimethylergolin-I (*I*)

Potassium (780 mg, 20 mmol) was added under nitrogen and with stirring at 35–40°C to a solution of 531 mg (2 mmol) compound *II* or of 527 mg (2 mmol) compound *III* in 30 ml phosphoric hexamethyltriamide. The mixture was stirred for 4 h, poured into 300 ml water, the product was filtered and washed with water (455 mg, 94.5%), m.p. 239–241°C. After crystallization from a mixture of chloroform and methanol (1 : 2) the compound melted at 242–243°C and had a $[\alpha]_D^{20}$ of -113° (c 0.25, pyridine), in agreement with data in the literature^{5,6}. Similarly¹⁴ in the region of 700–3800 cm^{-1} the compound exhibited the same IR spectrum (Nujol). In thin-layer chromatography (see ref.²), it has the same R_F as the authentic preparation.

The aqueous mother liquor after separation of crude festuclavine was shown argentometrically to contain 122.21 mg potassium cyanide (94.1%).

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