New Synthesis of Clavines: Determination of the Structure of Costaclavine by Nuclear Magnetic Resonance Spectroscopy

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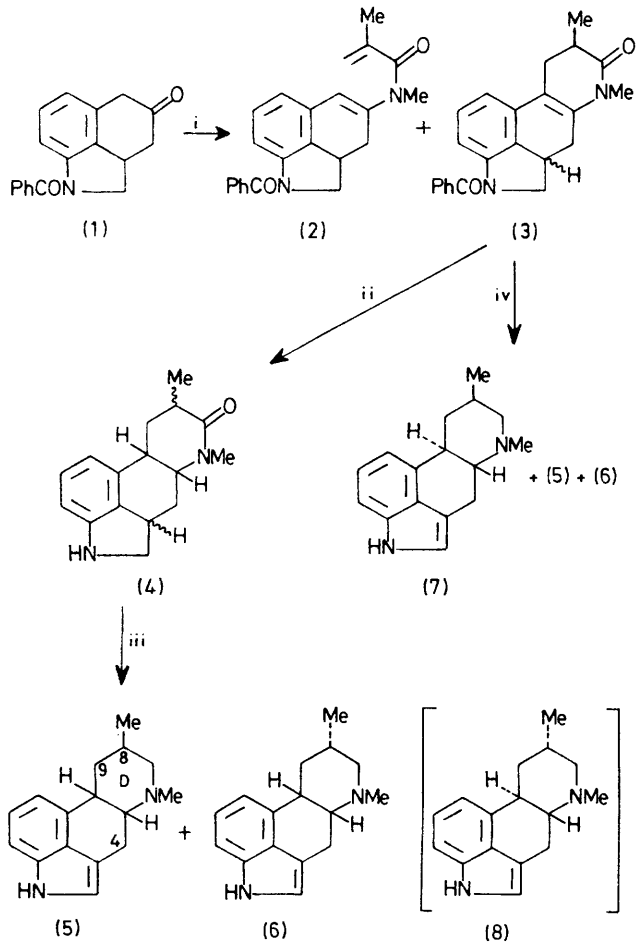
Summary The epimeric 6,8-dimethylergolines (**5**)—(**7**) have been prepared from a common key intermediate lactam (**3**); the structure of costaclavine has been established as (**5**) from the n.m.r. spectra of compounds (**5**)—(**8**).

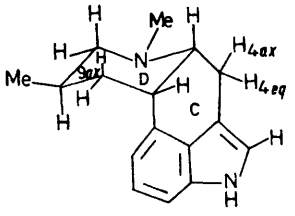
COSTACLAVINE is an alkaloid, first isolated from the saprophytic culture of the agropyrum-type ergot fungus[1a] and later obtained chemically by the reductions of agroclavine and elymoclavine.[2] On this basis structure (**5**) was proposed, although its stereochemistry still remained to be

determined. We now report on easy synthesis of costaclavine and its epimer; from the n.m.r. spectra of the clavines (**5**)—(**8**), the stereochemistry of costaclavine has been assigned.



Reagents: i, a, $MeNH_2$; b, $H_2C{=}CMeCOCl$; ii, a, PtO_2–H_2; b, HCl; iii, a, $LiAlH_4$; b, MnO_2; iv, a, $LiAlH_4$; b, Na–NH_3; c, MnO_2.

The reaction of the imine prepared from the benzindole (**1**),[4,5] with methacryloyl chloride under Hickmott's conditions[6] gave a 4:1 mixture of the cyclised lactam (**3**), ν_{max} 1650 cm^{-1}, and the uncyclised enamide (**2**), detected by n.m.r. spectroscopy, in 66% yield. Without purification, this mixture was hydrogenated (PtO_2–5 atm H_2; room temp.). The benzoyl group was removed by hydrolysis, and the saturated lactam (**4**), 24%, m.p. 246—248 °C, ν_{max} 1620 cm^{-1}, was obtained. The n.m.r. spectrum showed that the product (**4**) consisted mainly of two epimeric compounds in a ratio of *ca.* 3:1. $LiAlH_4$ reduction of (**4**), followed by dehydrogenation with MnO_2 afforded, upon separation by preparative t.l.c., two ergolines, (**5**), 16%, m.p. 183—185 °C, and (**6**), 5%, m.p. 132—135 °C. Compound (**5**) was identical (direct comparison) with natural costaclavine[1a] while n.m.r., i.r., and mass spectral data suggested that (**6**) was an epimer of costaclavine with respect to the 8-methyl configuration. This fourth isomer (**6**) of 6,8-dimethylergoline might exist in nature, and we have tentatively designated its name as epicostaclavine.



Structure of costaclavine (**5**).

When the lactam (**3**) was reduced successively with $LiAlH_4$ and Na in liquid NH_3, the crystalline *trans*-clavine (**7**), 2% from (**3**), m.p. 235—238 °C, was obtained, which was identified (direct comparison) as festuclavine;[1b] (**5**) and (**6**) were also detected by g.l.c. in the mother liquor. In view of ambiguities remaining about the stereochemistry of costaclavine,[2] we also examined the n.m.r. spectra of the four clavines (**5**)—(**8**) at 90 MHz using decoupling techniques. The results, and the resulting conformational conclusions, are summarised in the Table. The chemical shifts of the 8-methyl group, and the coupling patterns of the 4*ax*-, 4*eq*-, and 9*ax*- protons of these isomers clearly show that in the two C/D *trans* clavines, (**7**) and (**8**), the 8-methyl group is in an equatorial configuration in festuclavine (**7**) and in an axial one in pyroclavine (**8**), as already

TABLE

Proton Chemical shifts (δ) and coupling constants (Hz)[a] (in parentheses)

Proton	Costaclavine (**5**)	Epicostaclavine (**6**)	Festuclavine (**7**)	Pyroclavine (**8**)
9*ax*-H	1·43 ddd (14, 11, 5)	1·20 br. q (12)	1·08 br. q (12)	1·67 td (12, 5)
4*ax*-H	2·88 ddd (15, 4, 2)	2·96 d (8)	2·68 dd (15, 11·5)	2·57 ddd (15, 12, 2)
4*eq*-H	3·20 dd (15, 4)		3·39 dd (15, 4·5)	3·40 dd (15, 4·5)
C-Me	0·93 d (6)	0·91 d (6)	0·99 d (6·5)	1·29 d (6·5)
N-Me	2·24 s	2·57 s	2·49 s	2·36 s

[a] Measured in $CDCl_3$ and in good agreement with those reported for related compounds (L. Zetta and G. Gatti, *Tetrahedron*, 1975, **31**, 1403). On irradiation of the 2-H signal (δ 6·77), the 4*ax* signal was reduced to dd (*J* 15 and 4 Hz).

established.[1,7] Costaclavine (**5**) has the conformation as shown with the indole ring in an axial orientation and the 8-methyl group in an equatorial orientation with respect to ring D, while epicostaclavine (**6**) has the 8-methyl group in an equatorial configuration.

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