THE SYNTHESIS OF AN ERGOPEPTIDE CYCLOL

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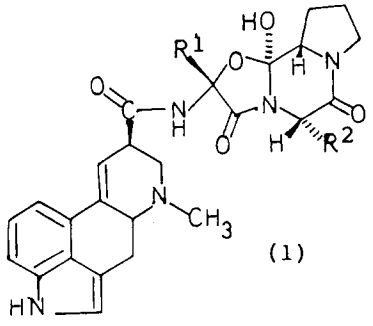
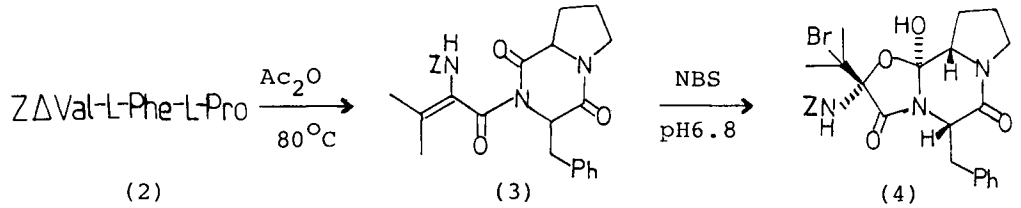
The ergopeptide alkaloids (1) are a group of naturally occurring compounds of unique structure in which lysergic acid is linked to a cyclol unit derived from cyclisation of a tripeptide. Recently Sibley and Creese (1983) studied the interactions of ergopeptide alkaloids with anterior pituitary D-2 dopamine receptors and have suggested that ergopeptides bind through their ergoline unit at the same site as other ligands and that the cyclol undergoes binding at an adjacent site and also provides most of the ligand- receptor binding energy. The substituents R^1 and R^2 in the cyclol are derived from the side chains in the parent tripeptide and each combination may cause the ergopeptide to assume different conformations and also possess different pharmacological profiles.



(1)

Our continuing interest in ergopeptide alkaloids has led us to develop a convenient synthesis of a bromocyclol with the intention of investigating its significance and potential when incorporated into an ergopeptide or linked to other bioactive molecules.

Treatment of N-benzyloxycarbonyl-$\alpha\beta$-dehydrovalyl-L-phenylalanyl-L-proline (2) with acetic anhydride at 80°C yielded the corresponding diketopiperazine (3), a proposed biosynthetic intermediate to cyclol formation. Recently Terashima et al (1977, 1979) reported a stereospecific ring closure of N-($\alpha\beta$-unsaturated) carbonylprolines to the corresponding halolactams by the addition of bromonium ion generated from N-bromosuccinimide (NBS). Treatment of (3) with NBS in dimethylformamide at pH 6.8 afforded the N-protected bromo-derivative of ergocristine cyclol (m/z 571, 573).



(2) (3) (4)

Deprotection by catalytic hydrogenolysis in the presence of one equivalent of HCl in methanol gave the bromocyclol hydrochloride. Bromine may be removed with tri-n-butyltin hydride and a free radical indicator (azo-bisisobutyronitrile, AIBN) in UV light to afford ergocristine cyclol. The free cyclols are stable only as their salts.

Sibley, D.R., Creese, I. (1983), Mol. Pharmacol. 23: 585.
Terashima, S. Jew, S.S. (1977), Tetrahedron Lett. 1005.
Terashima, S. et al (1979), Tetrahedron 35, 2337.