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CONVERSION OF AGROCLAVINE TO LYSERGOL

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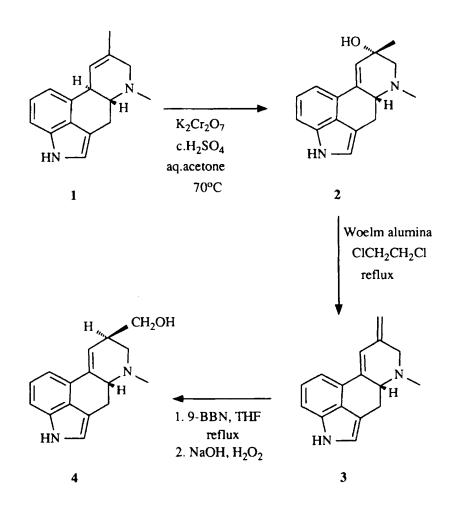
<u>Abstract</u>: The conversion of agroclavine (1) to lysergol (4) has been achieved in three steps utilising the dehydration of setoclavine (2) to lysergene (3).

Agroclavine¹ (1) is a readily available clavine alkaloid isolated from fermentations of *Claviceps purpurea* AA218². Its pharmacological properties in the central nervous system³ have led us to investigate analogues as potential antipsychotic agents⁴. As part of this aim we needed to functionalise the 8-methyl group of agroclavine. This led to the development of the previously unreported conversion of agroclavine to lysergol.

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SCHEME 1



The approach we took to the synthesis of lysergol originated from the established oxidation of agroclavine to setoclavine⁵. The envisaged regioselective dehydration of the clavine alcohol to give lysergene⁶ would allow selective hydration of the exocyclic double bond using hydroboration chemistry. Although the literature gave no direct examples of these transformations, the

work of Cymerman Craig⁷ on simplified ergot analogues did provide encouragement: this described a conversion of an indan analogue of lysergene to the corresponding analogue of lysergol using 9-BBN.

Agroclavine (1) was oxidised to setoclavine (2) by the literature procedure. Initial direct attempts at dehydration of the tertiary alcohol in setoclavine using $c.H_2SO_4$, I_2 or heating in DMSO led to decomposition or no reaction. An attempt at esterification was unsuccessful and *in situ* formation and elimination of sulphonic esters such as the tosylate, mesylate and triflate led to complex mixtures. Dehydration was finally accomplished by heating under reflux with pre-dried Woelm alumina N-super 1 (type W200)⁸ in 1,2 dichloroethane to give lysergene (3). The exocyclic double bond in lysergene was selectively hydroborated with 9-BBN at 60^OC in THF. Treatment of the adduct with aqueous sodium hydroxide and 30% hydrogen peroxide gave lysergol (4).

EXPERIMENTAL

Lysergene (3)

A suspension of Woelm alumina W200N act.1 (30g dried at 300^oC for 3 days) and setoclavine (2) (1g) in dry toluene was heated at reflux under an atmosphere of nitrogen for 2.5h. The reaction mixture was cooled, filtered and washed with carbon tetrachloride. The residue was added to a prepared column of alumina (N, act.3) and eluted with chloroform to give lysergene (3) as a white solid 0.34g. ¹H NMR[300MHz, DMSO-d₆] δ 10.75(1H,ex,NH), 7.21 and 7.17(2H,2d,12- and 14-H), 7.08(1H,t,13-H), 7.07(1H,br s,9-H), 6.93(1H,s,2-H), 5.00 and 4.90(2H,2 s,C=CH₂), 3.43 and 3.04(2H,2 d,7-H₂), 3.10(1H,dd,5-H), 3.45 and 2.50(2H,2dd,4-H₂) and 2.44(3H,s,NMe). ¹³C NMR⁹ [300MHz DMSO-d₆] δ 140.4(8-C), 136.1(10-C), 133.3(15-C), 126.3(11-C), 125.6(16-C), 121.8(13-C), 120.6(2-C), 119.0(9-C), 111.0(12-C), 109.7(14-C), 109.5(17-C), 108.3(3-C), 61.4(5-C), 57.7(7-C), 42.1(6-NMe), 26.0(4-C). (confirmation of

proton and carbon chemical-shift assignments was obtained from the ¹H-¹³C correlation spectrum).

Lysergol (4)

A solution of 9-BBN in dry tetrahydrofuran (0.5M, 1.89ml) was added dropwise to a stirred solution of lysergene (3) (74mg, 0.314mmol) in dry tetrahydrofuran (10ml) under an atmosphere of nitrogen at room temperature. The reaction mixture was heated at 60°C for 24h, cooled to 5°C and then ethanol (0.5ml), aqueous sodium hydroxide (2M, 0.25ml) followed by aqueous hydrogen peroxide (30%, 0.18ml) were added dropwise. The reaction mixture was stirred at 40°C for 2h, concentrated under reduced pressure, diluted with water and extracted with ethyl acetate (2X). The combined organic extracts were washed with a saturated solution of sodium chloride, dried over magnesium sulphate, filtered and evaporated under reduced pressure. The residue was purified by flash chromatography on silica (eluent ethyl acetate/methanol 4%,10%) to give lysergol (4) as a solid (48mg). ¹H NMR [300MHz MeOH- d_A) δ 7.17 and 7.11(2H,2d,12- and 14-H), 7.07(1H,t,13-H), 6.95(1H,s,2-H), 6.41(1H, br s, 9-H), $3.64(1H, dd, 17\alpha - H)$, $3.57(1H, dd, 4\beta - H)$, $3.54(1H, dd, 17\beta - H)$, 3.24(1H,dd,5-H), 3.19(1H,dd,7β-H), 2.88(1H,m,8-H), $2.68(1H, dd, 4\alpha - H),$ 2.64(3H,s,NMe), 2.38(1H,dd,7 α -H). ¹³C NMR [300MHz MeOH- d_{A}] δ 137.5(15-C), 136.8(10-C), 129.6(16-C), 128.4(11-C), 124.7(13-C), 123.1(9-C), 121.0(2-C), 113.6(12-C), 111.8(14-C), 111.3(3-C), 66.4(17-C), 66(5-C), 59.1(7-C), 45.0(6-NMe), 40.7(8-C), 28.7(4-C).

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