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CONVERSION OF AGROCLAVINE TO LYSERGOL

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

Agroclavine[1] (**1**) is a readily available clavine alkaloid isolated from fermentations of *Claviceps purpurea* AA218[2]. Its pharmacological properties in the central nervous system[3] have led us to investigate analogues as potential antipsychotic agents[4]. 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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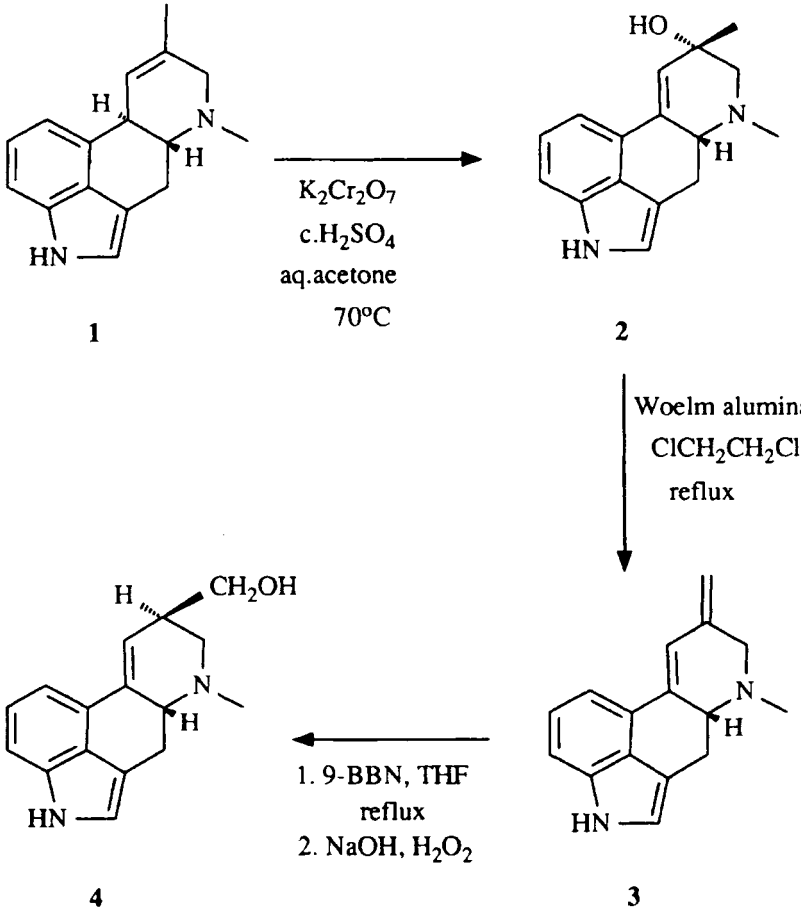
SCHEME 1



The approach we took to the synthesis of lysergol originated from the established oxidation of agroclavine to setoclavine[5]. The envisaged regioselective dehydration of the clavine alcohol to give lysergene[6] 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 Craig[7] 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°C 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°C 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. ^{1}H NMR[300MHz, DMSO-d_6] 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=CH_2), 3.43 and 3.04(2H,2 d,7-H_2), 3.10(1H,dd,5-H), 3.45 and 2.50(2H,2dd,4-H_2) and 2.44(3H,s,NMe). ^{13}C NMR[9] [300MHz DMSO-d_6] 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 ^{1}H-^{13}C 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). ^{1}H NMR [300MHz MeOH-d_4) 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,17α-H), 3.57(1H,dd,4β-H), 3.54(1H,dd,17β-H), 3.24(1H,dd,5-H), 3.19(1H,dd,7β-H), 2.88(1H,m,8-H), 2.68(1H,dd,4α-H), 2.64(3H,s,NMe), 2.38(1H,dd,7α-H). ^{13}C NMR [300MHz MeOH-d_4] 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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