A Facile Synthesis of 8-Hydroxy Lysergine from Lysergol

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Abstract- *8-hydroxy lysergine is prepared from commercially available lysergol. The synthesis involves reaction of lysergol with conc. H_2SO_4 resulting in the formation of 8-hydroxy lysergine in 48% yield.*

Keywords- Lysergol, H2SO4, 8-hydroxy lysergine.

I. INTRODUCTION

Ergot and ergot alkaloids have had medical importance for a long time [1]. They are used in the treatment of uterine atonia, postpartum bleeding, orthostatic circulatory disturbances, migraine, senile cerebral insufficiency, hypertension, acromegaly, hyperprolactinemia, and Parkinsonism [2-10]. Recently, new therapeutic applications of ergolines have emerged, e.g. against schizophrenia, and for therapeutic usage based on newly discovered antibacterial and cytostatic effects. Their structure is similar with several neurotransmitters and thus wide-scale physiological importance makes them a very interesting group of metabolites for the development of future medicines [1, 11]. Due to their property of selectivity with poly functional molecules and biological systems, they have advantages over many chemical reagents which cannot distinguish between multiple similar functional groups [12].

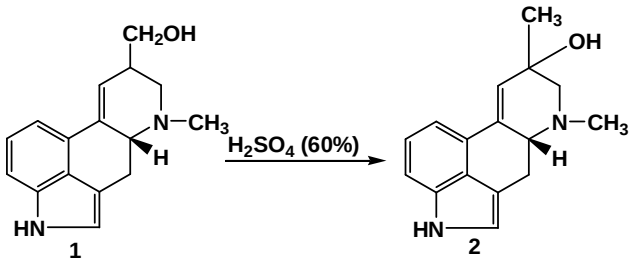
There has been a continuous effort towards the search for the synthesis of new ergot alkaloids and the synthesis of classically known ergolines by new methods. In this exploration various approaches have been taken. The first approach is bioconversion of ergolines. In nature several ergolines are inter-converted. These ergolines can be obtained by direct isolation or fermentation in trace amounts which is insignificant in front of their demand.

The second approach is total chemical synthesis of ergot alkaloids and their analogs with improved biological properties. This involves a stepwise and linear approach for the synthesis of target molecule. But, reported total syntheses are lengthy and give lesser yield of the target molecules.
The third approach is the inter conversion of naturally abundant ergoline to less abundant ergoline. This approach is used extensively to exploit an abundant supply of natural alkaloids. A significant number of ergolines is semi synthetically prepared whose production is based on few precursors e.g. lysergol, lysergic acid, 9,10- dihydrolysergol, and elymoclavine etc. [13].

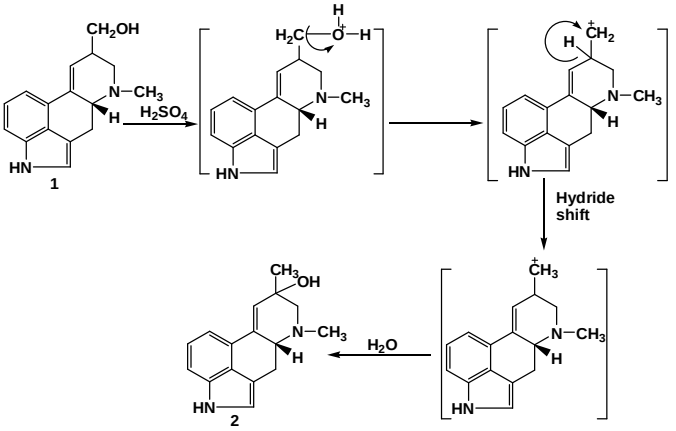
One of the important members of ergot alkaloids is lysergol. It has been isolated from *Ipomoea muricana* in 0.5 % overall yield [14-16]. Lysergol and lysergine and their minor alkaloids occur in *Claviceps* culture also [17-18]. But, their abundance is very less. It is interesting to synthesize less abundant from the more abundant ergolines, thus aiding relay synthesis in addition to total synthetic works. Keeping these factors in view, in the present work, the synthetic transformations of ergolines is planned to obtain lesser abundant ergolines. Therefore, the aim of the present work is to conversion of lysergol to 8- hydroxy lysergine.

II. RESULTS AND DISCUSSION

The reaction of lysergol **(1)** with sulphuric acid [19] afforded 8-hydroxy lysergine **(2)**. The proposed mechanism of the reaction is given in scheme 1. It is proposed that the protonation of hydroxyl group gives primary carbocation at C-17 (scheme 2). As secondary carbocation is more stable than primary carbocation, therefore, hydride shift takes place from C-8 to C-17. The addition of water according to Markonikoff's rule resulted in the hydroxylation at C-8. The ^{1}H NMR of the product (**2)** showed a multiplet at δ 0.8 ppm for three methyl protons at C- 17. A singlet for H-8 of lysergol at δ 2.67 ppm disappeared in the product. The ^{13}C NMR spectrum of the product 8-hydroxy lysergine **(2)** showed peaks at δ 68 ppm for C-8.



Scheme 1: Reaction of lysergol **(1)** with sulphuric acid to give 8-hydroxy lysergol **(2)**.



Scheme 2: Proposed mechanism for the dehydration of lysergol.

III. CONCLUSION

In the present work commercially available ergot alkaloid lysergol is converted to 8-hydroxy lysergine in 48% yield. The reaction is carried out in the presence of concentrated sulphuric acid. The mechanism of the reaction has been proposed and explain.

IV. EXPERIMENTAL

General: Melting points (°C) (m.p) were taken in open capillaries are uncorrected. Infrared spectra (IR) were recorded using Perkin Elmer Model 1430 spectrophotometer with potassium bromide (KBr) palette. Only principle absorption bands of interest are reported and expressed in cm^{-1}. NMR spectra were recorded using BRUKER AVANCE II 400(400MHz). Chemical shifts are given in ppm relative to tetramethyl silane as an internal standard (δ= 0 ppm) for ^{1}H NMR and DMSO-d_6 (δ= 39.50ppm) for ^{13}C NMR spectra.

8-Hydroxy lysergine (26): Concentrated sulphuric acid (65 mL) was added to lysergol (0.200 g, 0.787 mmol). The reaction mixture was refluxed for 4 h. After reaction completion, potassium hydroxide solution (20 %) was added slowly drop wise to raise the pH of the reaction mixture to ≈ 9. The reaction mass was extracted with ethyl acetate (3 × 25 mL). The combined organic layers were washed with brine (15 mL), dried over sodium sulphate and evaporated to give black residue. The residue obtained was recrystallized from methanol to give dark brown powder (0.961g).

IR (Nujol): 3410, 3269, 2848, 2921, 2383, 2253.70, 2127, 1657, 1466, 1402, 1050, 1025, 1005, 824, 763, 470.

^{1}HNMR (DMSO-d_6/ $CDCl_3$, 300MHz, δppm): 0.809 (m, 3H, H-17), 1.91 (s, 3H, N-CH_3), 2.51 (m, 1H, H-5), 2.74 (m, 2H, H-4), 6.96 (d, J= 9.7 Hz, 1H, H-2), 7.06 (m, 1H, H- 14), 7.13 (m, 1H, H-13), 7.22 (m, 1H, H-12).

^{13}CNMR (DMSO-d_6/ $CDCl_3$, 75MHz, δppm): 28.8 (C-4), 26.57 (C-18), 42.35 (N-CH_3), 63.11 (C-5), 67.89 (C-8), 110.9 (C- 3), 111.66 (C-14), 112.45 (C-12), 121.97 (C-13).

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