- A TOTAL SYNTHESIS OF (±)-LYSERGOL,
- A 9-ERGOLENE TYPE OF ERGOT ALKALOID

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<u>Abstract</u> — According to the synthetic route established on the despyrrole analog of the alkaloid, the first total synthesis of  $(\pm)$ -lysergol was completed.

In continuation of our synthetic work<sup>1-4</sup> on ergot alkaloids aiming at the synthesis of as many alkaloids as possible of having similar type of structures, we now report another first total synthesis of a member of ergoline type of alkaloids,  $(\pm)$ -lysergol  $(\underline{1})$ , via the route established by using the corresponding despyrrole derivatives with the  $\underline{\text{trans-1}}$ , 3-diol (7a) as the key intermediate.

## Synthesis of Despyrrololysergol (5b)

As in our recent total synthesis of lysergic acid, 1,2 the photocyclized lactam was converted into the <u>trans</u>\*1-hydroxy-2-aldehyde (2) which was used as the starting compound for the establishment of the synthetic route to lysergol. Sodium borohydride reduction of 2 yielded the <u>trans</u>\*1,3-diol (3a) which was acetylated under an ice-cooling temperature to give the corresponding monoacetate (3b), mp 141-142°C.

Chlorinative conversion of  $1\alpha$ -hydroxy group in 3b was carried out by the treatment of thionyl chloride in benzene to afford the  $1\alpha$ -chloride (4a) in 31% yield and the desired  $1\beta$ -chloride (4b) as the major product in 61% yield respectively. Their structures were readily established from their n.m.r. spectra, particularly from the signals of protons at 1-position, as a triplet (J=11 Hz) at  $\delta$  4.20 in 4a while as a broad singlet at  $\delta$  5.08 in 4b. Treatment of the  $1\beta$ -chloride (4b) with DBU in benzene under refluxing temperature effectuated dehydrochlori-

nation to yield the 9-ergolene type of compound (5a) in 95% yield which showed an olefinic proton signal at 1-position as a broad singlet at  $\delta$  6.13 thus confirming its structure. Acid hydrolysis of the acetate (5a) afforded the unsaturated alcohol (5b), mp 123-125°C, homogeneously which has a structure corresponding to the despyrrole analog of the alkaloid lysergol, thus established a potent synthetic route to the target alkaloid.

## Total Synthesis of $(\pm)$ -Lysergol $(\underline{1})$

According to the synthetic route established as above, total synthesis of the alkaloid ( $\pm$ )-lysergol was carried out starting from the key intermediate,  $\pm rans^{\pm}$  9-hydroxy-8-aldehyde ( $\pm$ ), which had been prepared from the photocyclized lactam and successfully used as the starting compound in the total synthesis of ( $\pm$ )-lysergic acid. Sodium borohydride reduction of  $\pm$  afforded the homogeneous  $\pm rans^{\pm}$ 1,3-diol (7a), mp 252-254°C (dec.), which was acetylated to give the monoacetate (7b), mp 215-218°C. The stereochemistry of this  $\pm rans$ -1,3-diol structure was clear from the n.m.r. peaks of two protons at 9- and 10-positions in the acetate (7b), which appeared as triplet with large coupling constant of about 10 Hz, respectively. Treatment of the monoacetyl-alcohol (7b) with thionyl chloride in benzene at 50°C for 1 h afforded the desired 9 $\pm$ 0-chloride ( $\pm$ 0) in 74 $\pm$ 1 yield. The stereochemistry of the 9 $\pm$ 1-chloride ( $\pm$ 0), particularly the 9 $\pm$ 2-configuration of the chloride, was confirmed by the n.m.r. signal of proton at 9-position appeared as a broad singlet at  $\pm$ 5.06.

DBU treatment of the 96-chloride (§) in benzene under reflux for 2 h yielded the unsaturated 9-ergolene type of compound (9a) which was then readily hydrolyzed with 10% hydrochloric acid under reflux for 1 h to yield dihydrolyzergol (9b) in 86% yield from §. The presence of an olefinic proton signal as a broad singlet at & 6.37 firmly established its structure (9b). Conversion of the indoline (9b) into the indole (1), therefore (±)-lyzergol, was achieved by the treatment with 0.5 equivalent of phenylseleninic anhydride<sup>5</sup> in the presence of 3 equivalents of indole under a nitrogen atmosphere at 40°C for 1.5 h to afford (±)-lyzergol (1), mp 220-224°C (dec.), in 97% yield. The comparison of n.m.r. and i.r. spectra, and t.l.c. of the synthetic compound (1) with those of (+)-lyzergol established their identity, thus completed the first total synthesis of the alkaloid.

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- \* Trans designation in the compounds, i.e. (2) and (6), represents the relative configuration of two substituents at 1- and 2- positions in 2 and at 8- and 9-positions in 6.
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