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

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Abstract ——— According to the synthetic route established on the despyrrole analog of the alkaloid, the first total synthesis of (±)-lysergol was completed.

In continuation of our synthetic work[1-4] 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, (±)-lysergol (1), via the route established by using the corresponding despyrrole derivatives with the 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 trans*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 trans*1,3-diol (3a) which was acetylated under an ice-cooling temperature to give the corresponding monoacetate (3b), mp 141-142°C.

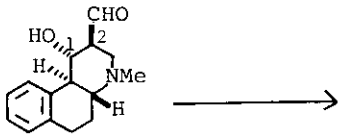
Chlorinative conversion of 1α-hydroxy group in 3b was carried out by the treatment of thionyl chloride in benzene to afford the 1α-chloride (4a) in 31% yield and the desired 1β-chloride (4b) as the major product in 61% yield respectively. Their structures were readily established from their n.m.r. spectra,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

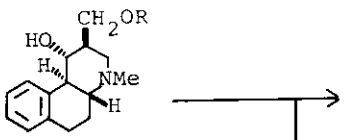
Total Synthesis of (±)-Lysergol (1)

According to the synthetic route established as above, total synthesis of the alkaloid (±)-lysergol was carried out starting from the key intermediate, trans*-9-hydroxy-8-aldehyde (6), which had been prepared from the photocyclized lactam and successfully used as the starting compound in the total synthesis of (±)-lysergic acid.[2] Sodium borohydride reduction of 6 afforded the homogeneous trans*-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 trans-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 9β-chloride (8) in 74% yield. The stereochemistry of the 9β-chloride (8), particularly the 9β-configuration of the chloride, was confirmed by the n.m.r. signal of proton at 9-position appeared as a broad singlet at δ 5.06.

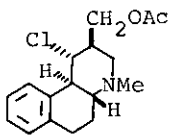
DBU treatment of the 9β-chloride (8) in benzene under reflux for 2 h yielded the unsaturated 9-ergolene type of compound (9a) which was then readily hydrolyzed with 10% hydrochloric acid under reflux for 1 h to yield dihydrolysergol (9b) in 86% yield from 8. The presence of an olefinic proton signal as a broad singlet at δ 6.37 firmly established its structure (9b). Conversion of the indoline (9b) into the indole (1), therefore (±)-lysergol, was achieved by the treatment with 0.5 equivalent of phenylseleninic anhydride[5] in the presence of 3 equivalents of indole[6] under a nitrogen atmosphere at 40°C for 1.5 h to afford (±)-lysergol (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 (+)-lysergol[7] established their identity, thus completed the first total synthesis of the alkaloid.



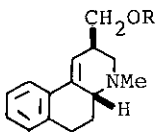
(2)



(3a) R=H
(3b) R=Ac



(4a)



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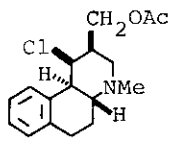
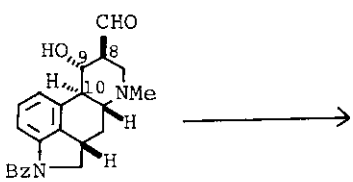
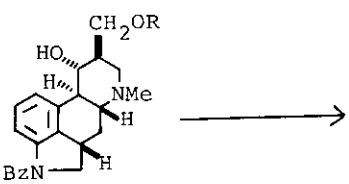
(5b) R=H



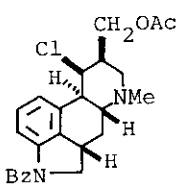
(4b)



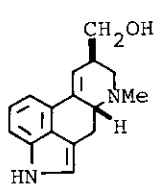
(6)



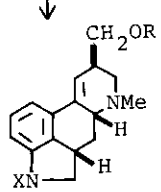
(7a) R=H
(7b) R=Ac



(8)



(1)



(9a) R=Ac, X=Bz
(9b) R=X=H

ACKNOWLEDGEMENTS

We are grateful to the collaboration of Misses Y. Yutsudo and Y. Yoshida. We also thank Dr. S. Agurell of Astra Läkemedel AB, Sweden for his generous gift of the precious sample of the alkaloid and Sir Derek H. R. Barton of Institut de Chimie des Substances Naturelles, Gif-sur-Yvette, France for his kind supply of the reagent and advice.

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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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6 Further results on the dehydrogenation with phenylseleninic anhydride in the presence of indole will be published elsewhere.

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Received, 20th February, 1985