## INTRODUCTION OF SUBSTITUENT ONTO 4-POSITION OF INDOLE NUCLEUS BY INTER-MOLECULAR CYCLIZATION OF $\alpha$ , $\beta$ -dehydrotryptophan methyl ester with aldehyde

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Summary: Intermolecular cyclization of  $\alpha$ ,  $\beta$ -dehydrotryptophan methyl ester **4**, with aldehydes afforded 5,6-dihydroazepino[5,4,3-cd]indole derivatives, **5a-c**, which contain the same ring system with clavicipitic acid (6).

In the biosynthesis of ergot alkaloids (3), <sup>1</sup> a prenyl group is first introduced at 4-position of tryptophan (Scheme 1). Although many attempts introducing such substituent at the position of tryptophan <u>directly</u> have been studied for a long time, no successful method was reported except a few cases.<sup>2-6</sup>

In our synthetic studies on indole alkaloids, we found an unusual cyclization<sup>7</sup> of protected neoechinulin A onto the 4-position of indole nucleus and further proved the applicability to a simple dehydrotryptophan derivative.<sup>8</sup> Now we report a intermolecular cyclization of dehydrotryptophan methyl ester  $\frac{4}{2}$  with satulated aldehydes.

Scheme 1. Biosynthesis of ergot alkaloids (3).



Dehydrotryptophan methyl ester **4** was synthesized by the method reported by Hengartner et al. **[4:** mp 137-138°C; MS m/z 216(M<sup>+</sup>); <sup>1</sup>H-NMR  $\delta$ (DMSO-d<sub>6</sub>) ppm 3.76(3H, s), 4.56(2H, br.s), 6.64(1H, s), 7.02(2H, m), 7.32(1H, m), 7.58(1H, m), 7.70(1H, s)]. Condensation of **4** with aldehydes were achieved in the presence of camphorsulfonic acid (CSA) or boron trifluoride etherate (BF<sub>3</sub>OEt<sub>2</sub>) and reaction conditions were shown in Table 1. After usual work up, pure cyclization products were obtained by chromatography on silica gel TLC as a major component. The structures were determined to be 5,6-dihydroazepino[5,4,3-cd]indole derivatives,**5a**-c, on the bases of their spectroscopic data [ for instance, **5c**; mp 162-163°C; MS m/z 284(M<sup>+</sup>); <sup>1</sup>H-NMR  $\delta$ (DMSO-d<sub>6</sub>) ppm 0.86(3H, d, J=7 Hz), 0.89(3H, d, J=7 Hz), 1.00-1.20(1H, m), 1.30-1.65(2H, m), 3.77(3H, s), 4.50(1H, m), 5.32(1H, br.s), 6.76(1H, d, J= 7 Hz), 6.94(1H, s), 7.03(1H, t, J=7 Hz), 7.25(1h, d, J=7 Hz), 7.50(1H, d, J=7 Hz)]. Cyclization products, **7a**-c, produced by Pictet-Spengler type cyclization, were not detected on silica gel TLC of the reaction mixture but small amount of further oxidized  $\beta$ -carboline derivatives were obtained in each cases.

One of the major reasons of such selectivities to cyclize onto 4-position of indole nucleus should be stabilization of pyrrole ring of intermediate I or II by conjugation with a conjugated ester group at 3-position. These intermolecular cyclization should be related to the biosynthesis of ergot



Table 1. Reaction conditions of 4, with aldehydes.

Reagent	Catalyst	Solvent	Temp.	Time	Product	Yield
CH2≠CHOCH2CH3	CSA	CH <sub>2</sub> Cl <sub>2</sub>	40°C	1 h	5a	34%
сн <sub>3</sub> сно	BF <sub>3</sub> OEt <sub>2</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	25°C	2 h	5a	21%
(CH <sub>3</sub> ) <sub>2</sub> CHCHO	BF3OEt2	(CH <sub>2</sub> Cl) <sub>2</sub>	80°C	13 min	5 <u>b</u>	41%
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CHO	BF <sub>3</sub> OEt <sub>2</sub>	(CH <sub>2</sub> Cl) <sub>2</sub>	80°C	13 min	5 <u></u> €	45%
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CHO	CSA	(CH <sub>2</sub> Cl) <sub>2</sub>	60°C	20 min	5 <u></u> €	39%

alkaloids. Further synthetic studies on ergot alkaloids and clavicipitic acid are now in progress.

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- 10. 5a: mp 160.5-161.5°C; MS m/z 242(M<sup>+</sup>); 5b: mp 168-169°C; MS m/z 270(M<sup>+</sup>). The structures of 5a,b,c were further confirmed by acetylation of 5a-c with Ac<sub>2</sub>O/Py to the corresponding mono and diacetates.
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