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INTRAMOLECULAR PHOTOCHEMICAL CLOSURE TO 4-TRYPTOPHAN-SUBSTITUTED TIGLATE DERIVATIVES

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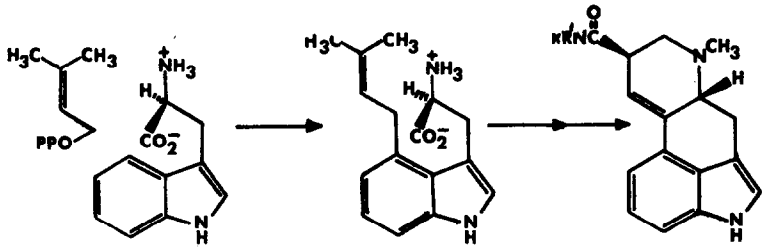
Attempts to simulate the initial biochemical step in the formation of the ergot alkaloids (Figure 1) have been remarkably unsuccessful; apparently the

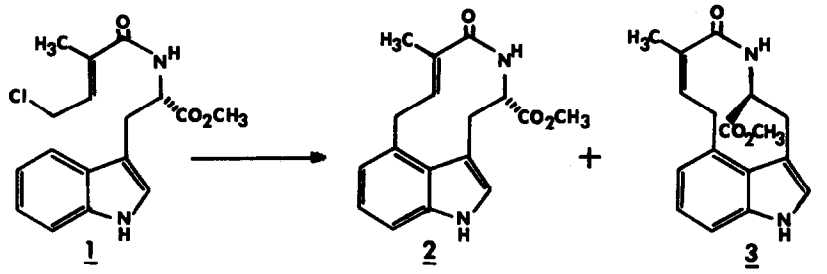
Figure 1



in vivo condensation of the dimethylallyl moiety to the 4-position of the tryptophan indole is strongly guided by spatial and structural constraints.[1] Continuing our studies on the interaction of functional groups along peptide chains,[2] we searched for a molecule in which intramolecular alkylation by the dimethylallyl side chain at the appropriate indole position would be spatially favored. γ-Chlorotiglyl L-tryptophan methyl ester, 1, seemed a good choice. Examination of a Büchi model of 1 in its *cis* amide form showed that the methylene of the tiglyl side chain may be placed directly above the C-4 of the indole, and is closer to this carbon than to any other atom of the indole

nucleus. Thus, we anticipated that alkylation would be favored at this position due to the restricted degrees of freedom imposed by the combination of

Figure 2



the conjugated amide and the indole. The product 2 and its double bond isomer 3 would have all the elements of the ergoline skeleton, excepting the C-D ring fusion bond. Inspired by the photochemical studies of Yonemitsu and Witkop,[3] we have photochemically cyclized amide 1 to two ten-membered lactams having the ergoline framework (Figure 2).

The required γ-chlorotiglyl L-tryptophan methyl ester 1[4] (mp 132.5-133.5°C) was prepared in 95% yield from γ-chlorotiglyl chloride[5] and L-tryptophan methyl ester in CH_2Cl_2 in the presence of $(iPr)_2EtN$. Compound 1 exhibited the following spectral data: NMR ($CDCl_3$) -- t of q, 6.32 δ, vinyl H; s, 3.72 δ, O-CH_3; and d, 1.85 δ, C-CH_3; IR ($CHCl_3$) -- 1738, 1668 and 1633 cm^{-1}; UV (95% EtOH) -- 2750, 2830 and 2910 Å (log ε = 3.80, 3.83 and 3.77); and m/e 336, 334, 201 and 130 (100%).

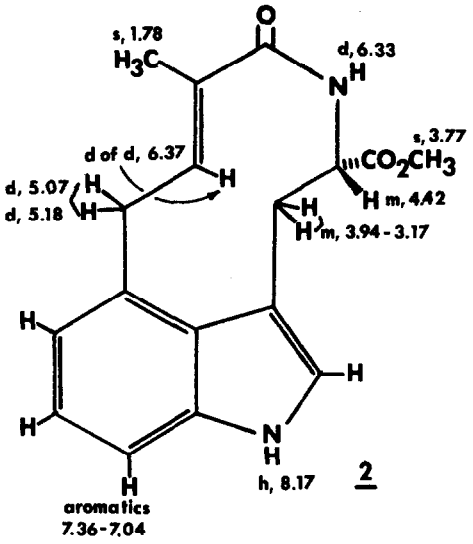
Photocyclization proceeded best in dry CH_3CN. After 6 hours irradiation at 2537 Å through vycor, starting amide 1 was gone. Through column chromatography on silica gel (elution with 0-4% EtOAc in CH_2Cl_2), one can isolate tiglyl lactam 2[4] (33.2%) (mp 231-232°C) and the less polar angelyl lactam 3[4] (19.3%) (mp 131.8-132.5°C). Compound 2 gave the following spectral data: NMR -- see Figure 3; IR ($CHCl_3$) -- 1740 and 1692 cm^{-1}; and UV (95% EtOH) -- 2900 Å, broad (log ε = 3.86). Compound 3 gave the following spectral data: NMR -- see Figure 3; IR ($CHCl_3$) -- 1740, 1693 and 1685 cm^{-1}; and UV (95% EtOH) -- 2770, 2830 and 2910 Å (log ε = 3.74, 3.75 and 3.71). Stereochemical assignment of the tiglyl and angelyl lactams 2 and 3 is based on the NMR trends observed by Plieninger et al.[6] with γ-(4-indolyl)-tiglates and angelates. Both amides 2 and 3 gave mass spectral peaks at m/e 298, 283, 266, 254, 239, 184 (100%), 168, 167, 156, 155 and 154. These are cleavage and cyclization patterns similar to those seen from N_α-methyl 4-dimethylallyl tryptophan[7] and the $\Delta^{8,9}$-clavine alkaloids, such as elymoclavine.[8] Lactam 3 can be hydrolyzed with $Ba(OH)_2$ to give a mixture of the two isomeric amino dicarboxylic acids

after isolation by ion exchange chromatography. Collectively, the above data show alkylation at C-4 of the indole.

We are directing the further investigation of this photocyclization towards compounds with additional synthetic and medicinal potential.

Figure 3

100 MHz NMR Data for $CDCl_3$ Solutions at 23°C.
Signal, resonance in δ.



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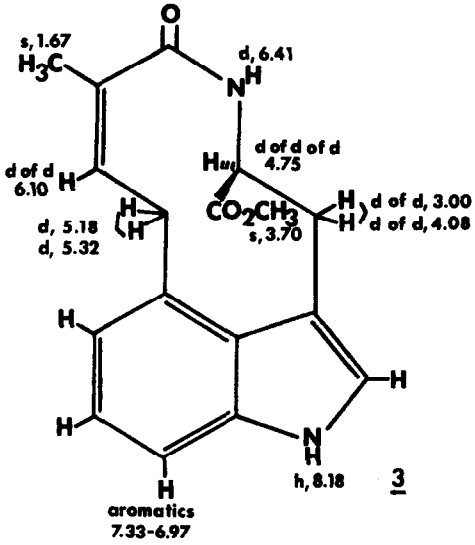

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