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A Stereochemical Test of the Mechanism of Electrophilic Substitution in 3-Substituted Indoles

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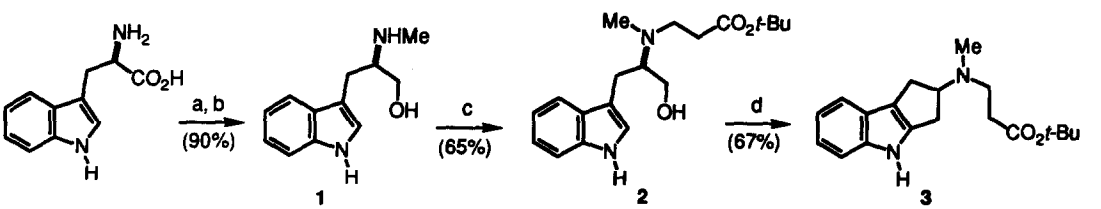
Abstract: A cyclization reaction that provides access to the cyclopent[b]indole ring system is reported. The stereochemical course of the reaction suggests the intermediacy of a 3,3-disubstituted indolenine.

The electrophilic substitution of 3-substituted indoles usually occurs at C-2.[1] In 1967, Jackson and Smith proposed that this reaction proceeds via the formation of a 3,3-disubstituted indolenine followed by a Wagner-Meerwein-like 1,2 shift.[2] Later, Casnati reported that direct alkylation of a 3-alkylindole at C-2 can effectively compete with formation of the 3,3-dialkyl indolenine.[3] In this Letter, we report a cyclization reaction that sheds light on this question, in that the two mechanisms–direct alkylation versus the indolenine pathway–predict differing stereochemical results.

In the course of synthetic studies directed towards lysergic acid, we prepared alcohol **1** in optically active form from D-tryptophan[4] (Scheme 1). Attempted mesylation of **1** yielded instead the tricyclic cyclopent[b]indole **3**.[5]

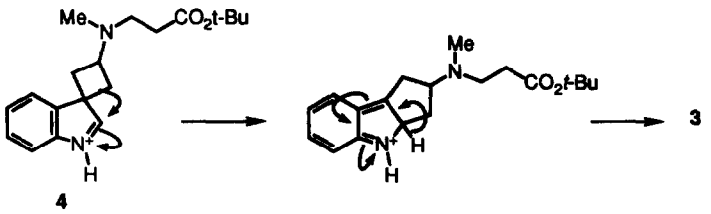
Scheme 1



a. $ClCO_2Et$, aq NaOH, 1 h. b. $LiAlH_4$, THF, Δ, 24 h. c. CH_2=$CHCO_2t$-Bu, MeOH, Δ, 10 h. d. MsCl, Et_3N, CH_2Cl_2, rt, 2.5 h.

Interestingly, **3** was devoid of optical activity. Although this result cannot be explained by cyclization occurring by direct attack at C-2, it is consistent with Jackson and Smith's mechanism for electrophilic substitution. In this case, one must invoke the intermediacy of a 4-membered ring[6] spiroindolenine **4** (Scheme 2), which possesses a mirror plane and is hence achiral. It is noteworthy that racemization occurs by the conversion of two non-equivalent groups in the starting material into equivalent ones, rather than by reaction at the stereocenter itself. The immediate precursor to **4** in this reaction is not known; the mesylate may be directly attacked by the indole ring, or may undergo prior attack by the exocyclic tertiary amine to give a transient aziridinium cation.

Scheme 2



These results suggest that the primary pathway for alkylation of 3-substituted indoles involves 3,3-disubstituted indolenines. Direct attack at C-2 is likely only with highly reactive substrates, such as allylic and benzylic halides or indoles with electron-rich substituents. Our cyclization also provides access to the cyclopent[b]indole ring system under mild and neutral reaction conditions. This ring system is part of the skeletal framework in a number of natural products, including the tremorgenic indole diterpene alkaloids and the anti-implantation monoterpene indole alkaloid yuehchukene.

Acknowledgement

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References and Notes

1. Sundberg, R. J. *The Chemistry of Indoles*; Academic Press: New York, 1970.

2. (a) Jackson, A. H.; Smith, P. *Chem. Comm.* **1967**, 264. (b) Jackson, A. H.; Naidoo, B.; Smith, P. *Tetrahedron* **1968**, *24*, 6119.

3. Casnati, G.; Dossena, A.; Pochini, A. *Tetrahedron Lett.* **1972**, 5277.

4. All new compounds were purified by recrystallization or flash column chromatography and fully characterized. Compound **1**: white solid, mp 80-82 °C. IR: 3440, 3330 cm^{-1}. ^1H NMR (400 MHz): δ 2.42 (s, 3), 2.88-2.97 (m, 3), 3.42 (dd, 1 , J = 4.3, 10.6), 3.71 (dd, 1, J = 3.4, 10.6), 7.04 (s, 1), 7.13 (t, 1, J = 7.0), 7.21 (t, 1, J = 7.1), 7.38 (d, 1, J = 8.1), 7.62 (d, 1, J = 7.8), 8.09 (s, 1). ^{13}C NMR (50 MHz): δ 26.91, 33.77, 60.71, 62.27, 111.22, 112.09, 118.66, 119.21, 121.90, 122.76, 127.47, 136.32. Compound **2**: pale yellow solid, mp 91-92 °C. $[\alpha]_D$ = −12.2 (c 1.0, $CHCl_3$). IR: 3250, 1730 cm^{-1}. ^1H NMR (250 MHz): δ 1.46 (s, 9), 2.40 (s, 3), 2.41-3.46 (m, 9), 6.98 (d, 1, J = 2.2), 7.12 (t, 1, J = 7.5), 7.20 (t, 1, J = 7.5), 7.36 (d, 1, J = 7.8), 7.57 (d, 1, J = 7.7), 7.99 (s, 1). ^{13}C NMR (50 MHz): δ 20.23, 28.02, 34.70, 36.10, 48.79, 60.89, 65.22, 80.68, 111.24, 112.46, 118.31, 119.06, 121.76, 122.13, 127.16, 136.25, 172.11.

5. Compound **3**: pale yellow oil. IR: 1730 cm^{-1}. ^1H NMR (250 MHz): δ 1.44 (s, 9), 2.30 (s, 3), 2.40 (t, 2, J = 7.2), 2.68-2.78 (m, 3), 3.03-3.12 (m, 2), 3.42 (dd, 1, J = 4.6, 15.1), 4.24 (m, 1), 7.10-7.39 (m, 3), 7.62 (d, 1, J = 7.7), 8.08 (s, 1). ^{13}C NMR (50 MHz): δ 28.08, 31.97, 33.68, 42.38, 53.45, 60.47, 63.67, 80.40, 111.16, 111.84, 118.65, 119.25, 121.81, 123.12, 127.49, 135.96, 171.85.

6. The strain present in a 4-membered ring has led to this mechanism being disfavored in an analogous cyclization: (a) Bergman, J.; Venemalm, L. *Tetrahedron Lett.* **1987**, *28*, 3741. (b) Bergman, J.; Venemalm, L.; Gogoll, A. *Tetrahedron* **1990**, *46*, 6067.

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