Pergamon

Tetrahedron Letters, Vol. 38, No. 49, pp. 8483-8486, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10306-9

Oxidation of Indolines with Fremy's Salt: A Mechanistic Proposal

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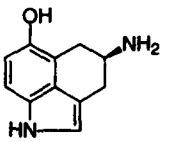
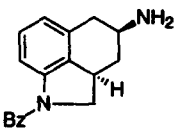
Abstract: Oxidation of an indoline with Fremy's salt (potassium nitrosodisulfonate) led to the formation of an unstable intermediate which isomerized to the desired 5-hydroxyindole upon standing. This intermediate has been isolated and characterized as an iminoquinone derivative. Identification of this intermediate has allowed us to propose a mechanism for the Fremy's salt mediated oxidation of indolines to 5-hydroxyindoles. © 1997 Elsevier Science Ltd.

During the course of our studies of serotonergic agents, we were interested in preparing the conformationally restricted serotonin analogue **1** and its enantiomer.[1] The synthesis of (±)-**1** has been reported in the patent literature; however the synthetic route is quite lengthy and no method for resolution of (±)-**1** has been reported.[2] Since we had ready access to both enantiomers of the indoline derivative **2**,[3] we felt the most direct route would involve an oxidative conversion of **2** to **1**. The key step in this conversion would involve a Fremy's salt mediated oxidation.



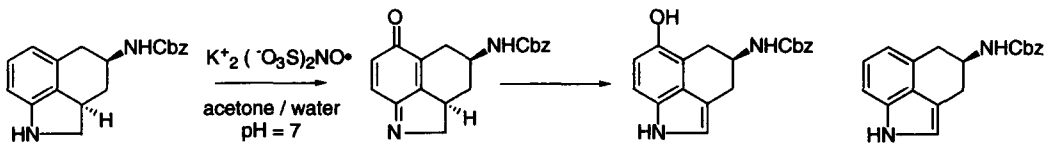
1



2

Fremy's salt (potassium nitrosodisulfonate) is a radical oxidizing agent which is most commonly employed to oxidize phenols to the corresponding benzoquinones.[4] We are also aware of a few reports where it has been used to convert indolines to the corresponding 5-hydroxyindoles.[5] No mechanism for this interesting reaction has been proposed, although Humber, *et al.* [5d] reported the formation of an uncharacterized intermediate which was transformed to the desired 5-hydroxyindole upon standing. We report in this communication the isolation and identification of an intermediate in this oxidation process which allows us to draw conclusions about the mechanism of this transformation.

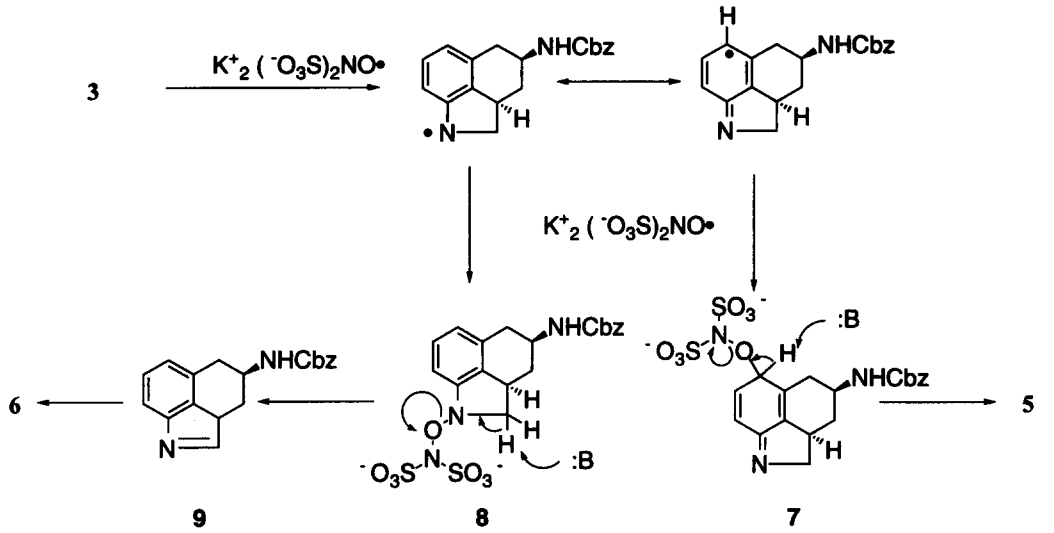
Basic hydrolysis of **2** followed by reaction with Cbz-Cl gave the indoline derivative **3**. A solution of **3** in acetone/water (buffered to pH = 7) was treated with 2 equivalents of an aqueous solution of Fremy's salt at room temperature. The purple color of the Fremy's salt solution was discharged after 15 minutes and **3** was no longer visible by tlc. Aqueous workup followed by rapid flash chromatography gave a red foam in moderate yield. Mass spectral analysis showed this product possessed a parent ion consistent with the expected hydroxyindole **4**, but the ^{1}H-nmr was clearly inconsistent with **4**.[6] Only seven aromatic protons were present instead of the expected eight aromatic protons and there were eight aliphatic protons in the region 1.0 - 5.0 ppm rather than the five expected for **4**. Additionally, the ir spectrum showed the presence of two carbonyl stretches at 1718 and 1636 cm^{-1} and there was a very strong uv absorbance at 271 nm. Based on these spectral data, we determined that this intermediate is the iminoquinone **5**. Upon standing at room temperature, either as a foam or in $CDCl_3$ solution, **5** underwent isomerization to hydroxyindole **4**[7] in high yield. When the Fremy's salt oxidation was run under basic conditions, we were able to isolate both the unsubstituted indole **6** and iminoquinone **5** from the crude reaction mixture.



3 **5** **4** **6**

The demonstration that the oxidation of indolines to 5-hydroxyindoles with Fremy's salt proceeds through the intermediate iminoquinone **5** allowed us to postulate a mechanism for this transformation (Scheme). By analogy with the mechanism proposed for the oxidation of phenols to benzoquinones,[4] we propose that the initial step is the abstraction of the N-1 hydrogen atom by Fremy's salt to provide the nitrogen radical. A number of resonance forms for this radical can be drawn. Trapping of this radical at C-6 with a second molecule of Fremy's salt gives intermediate **7** which can undergo N-O cleavage with loss of a proton to yield the iminoquinone **5**. This product then undergoes tautomerization to the more stable hydroxyindole **4**. There is ample precedent for the last step in this transformation. Kita, et al have developed a synthesis of 5-hydroxyindoles from 2-(2-aminoethyl)-benzoquinone in which an iminoquinone intermediate tautomerizes to form the final product.[8] The unsubstituted indole **6** results from trapping of the initially formed radical at N-1 with Fremy's salt to give intermediate **8** which undergoes loss of N,N-disulfonylhydroxylamine to give indolenine **9** which tautomerizes to **6**. Thus, both reaction products can be readily accounted for by this mechanism.

Scheme



The identification of **5** as an intermediate in the formation of hydroxyindole **4** not only answers a mechanistic issue but also has synthetic consequences. While **4** and **5** are tautomers, their chemical reactivities differ considerably. The reactions of iminoquinones like **5** will be discussed in subsequent papers.

Experimental procedure: A solution of potassium nitrosodisulfonate (0.37g, 1.48 mmol) in pH 7 phosphate buffer (10 mL) and distilled H_2O (25 mL) was added to a stirred solution of **3** (200 mg, 0.65 mmol) in acetone (25 mL) at room temperature. Fifteen min after the addition, the reaction mixture was extracted with $CHCl_3$ (3 x 50 mL). The combined $CHCl_3$ layers were washed sequentially with distilled H_2O (50 mL) and brine (50 mL) and then dried (Na_2SO_4) and concentrated to afford 220 mg of crude product. Flash chromatography (1:1 hexane:EtOAc and then EtOAc) afforded **5** as a red foam (120 mg, 57 %).[6] This material was allowed to stand at room temperature overnight. Purification by flash chromatography (7:3, hexane:EtOAc) provided **4** as an off-white foam (82 mg, 69 % from **5**). Recrystallization from isopropanol gave an analytical sample (mp = 60°).[7]

Acknowledgment: We would like to thank Dr. Michael Martinelli (Lilly Research Laboratories) for generously supplying **2**. We also thank Professor Camille Wermuth and Dr. Andre Mann of the Universite Louis Pasteur, Strasbourg for stimulating discussions and advice. B. G. also thanks Eli Lilly and Company for a postdoctoral fellowship.

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6. ^{1}H NMR (300 MHz, $CDCl_3$): 1.23 (q, 1H, J= 11.7, H_{4a}); 2.02-2.12 (m, 1H, H_{4b}); 2.40-2.55 (m, 1H, H_{6a}); 2.90-3.10 (m, 2H, H_{6b} and H_3); 3.83 (d, 1H, J= 18.5, H_{2a}); 3.95-4.10 (m, 1H, H_5); 4.66 (dd, 1H, J= 18.5, 6.8, H_{2b}); 4.87 (d, 1H, J= 7.2, -NH-); 5.11 (s, 2H, $-CH_2-$); 6.58 (d, 1H, J= 9.9, H_8), 7.20-7.40 (m, 6H, H_9 and $-C_6H_5$).
Mass: m/z 322.2 (M^+).
IR ($CHCl_3$): 3480, 3010, 1718, 1636, 1509, 1268 cm^{-1}.
UV-Vis (MeOH): 271 nm (log ε 4.14), shoulder to 400 nm.
7. ^{1}H NMR (300 MHz, d^6-DMSO): 2.40-2.65 (m, 2H, H_{3a} and H_{3b}); 2.94 (dd, 1H, J= 11.4, 4.6, H_{5a}); 3.10 (dd, 1H, J= 11.4, J= 4.6, H_{5b}); 3.75-3.85 (m, 1H, H_4); 5.05 (s, 2H, $-CH_2-$); 6.58 (d, 1H, J=8.4, H_7); 6.87 (s, 1H, H_2); 6.88 (d, 1H, J=8.4, H_8), 7.30-7.45 (m, 5H, $-C_6H_5$); 7.43 (d, 1H, J= 7.8, -NH-CO); 8.36 (s, 1H, -NH-); 10.3 (s, 1H, -OH). ^{13}C NMR (d^6-DMSO): 28.31, 29.12, 48.40, 65.16, 108.63, 109.36, 111.68, 112.44, 119.17, 127.31, 127.71, 128.10, 128.21, 128.32, 137.21, 154.21, 155.48.
Mass: m/z 322.2 (M^+).
IR ($CHCl_3$): 3481, 3429, 3010, 1711, 1508, 1445 cm^{-1}.
UV-Vis (MeOH): 301 nm (log ε 3.62), 276 (log ε 3.73).
Found: C, 69.64; H, 5.97; N, 8.33. $C_{19}H_{18}N_2O_3$ requires C, 70.19; H, 5.63; N, 8.69.
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(*Received in USA* 29 *August* 1997; *revised* 29 *September* 1997; *accepted* 30 *September* 1997)