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SYNTHETIC STUDIES ON PARAHERQUAMIDE: REGIOSELECTIVITY OF INDOLE OXIDATION

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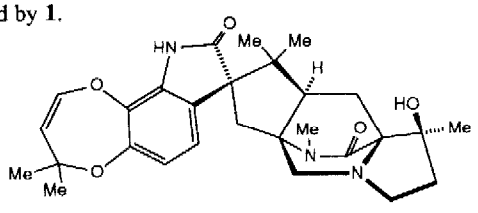
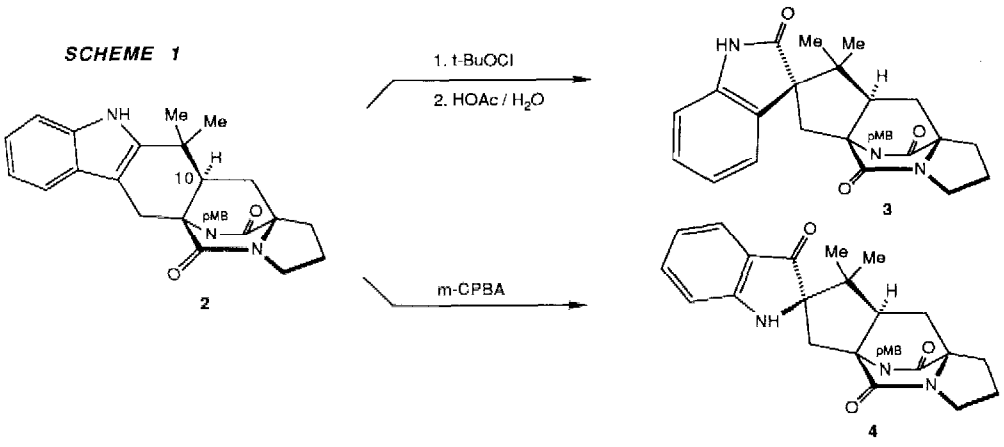
Summary: *Oxidation of indole 2 with tert-butyl hypochlorite followed by hot acetic acid affords a spiro 2-oxindole 3 which serves as a model for the total synthesis of paraherquamide.*

Paraherquamide (**1**) is a mycotoxic alkaloid obtained from *Penicillium paraherquei.*[1] The unusual structure[2] of this complex alkaloid has been secured by single crystal x-ray analysis[1] and the absolute configuration of **1** has been obtained by an x-ray structural analysis of a semi-synthetic degradation product.[3] Interest in this unusual, small class of alkaloids has recently been fueled by the observation of a Merck group[4] that **1** possesses potent anti-parasitic properties. Studies dealing with totally synthetic efforts to assemble this heptacyclic alkaloid have not yet appeared. In this paper, we detail a model study that embraces both regio- and stereochemical challenges posed by **1**.



1, *PARAHERQUAMIDE*

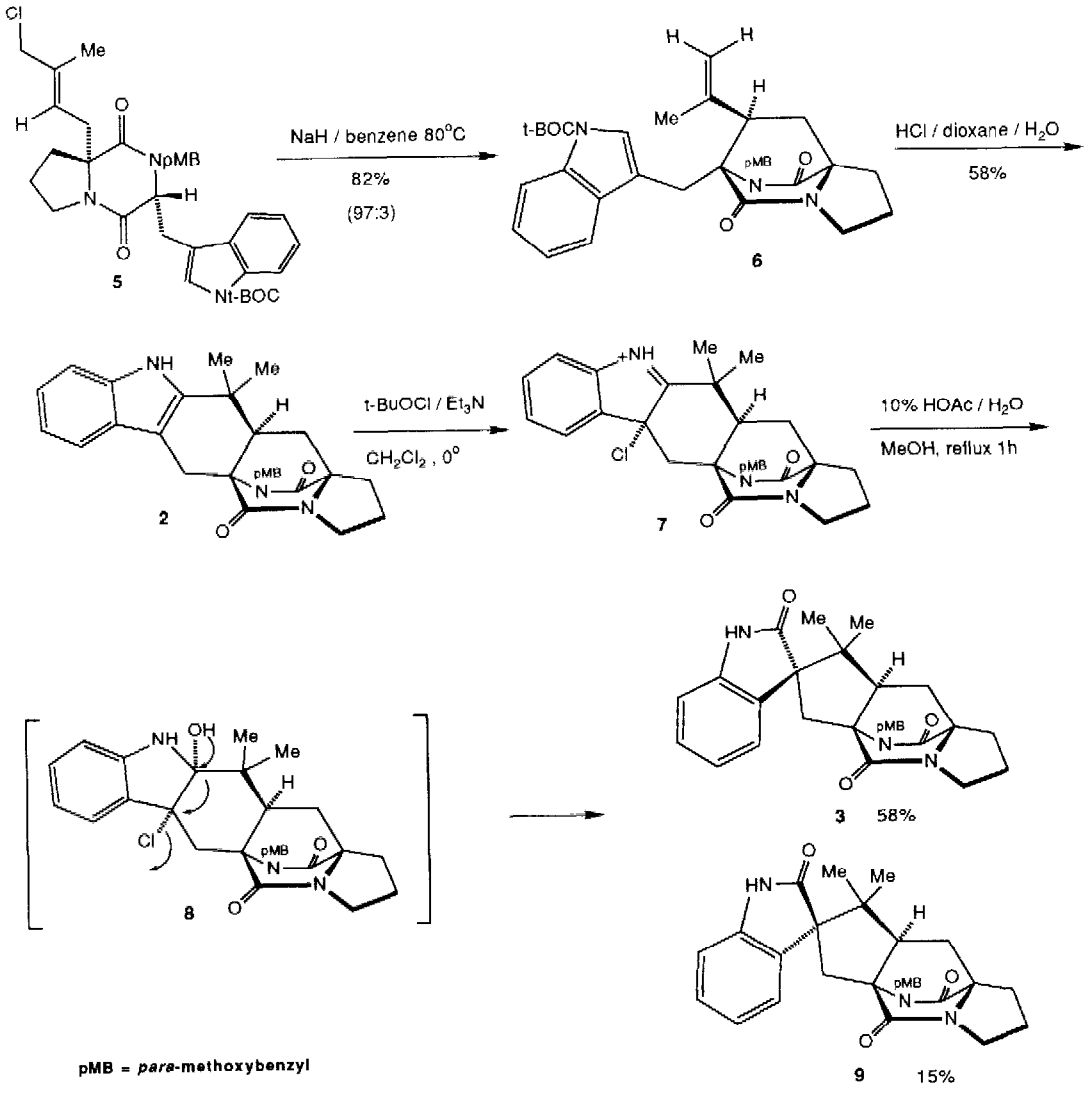
We recently reported[5] the highly stereoselective S_N2' cyclization of **5** to the tricyclic system **6** (97:3 ratio, 82%). Cyclization of **6** with aqueous HCl in dioxane afforded the crystalline substance **2** (58%).[5c] It was observed[5b,c] that treatment of **2** with m-CPBA in dilute CH_2Cl_2/THF solution proceeded in a highly stereoselective manner to afford (after base-induced rearrangement of the incipient 3-hydroxyindolenine) the corresponding spiro 3-indoxyl (**4**, Scheme 1). It seemed that such a 2,3-disubstituted indole (**2**) should serve as a reasonable type of synthetic precursor to the isomeric spiro 2-oxindole moiety of **1**. However, to achieve such a transformation, oxidation would have to be directed at the more hindered 2-position which is flanked by the adjacent gem-dimethyl groups. Literature precedent[6] revealed that oxidation with *tert*-butyl hypochlorite should



display the desired regio- as well as face selectivity for construction of the paraherquamide ring system. In the event (Scheme 2), treatment of **2** with *tert*-butyl hypochlorite in CH_2Cl_2 at 0°C followed by treatment with hot aqueous acetic acid provided, after workup, the oxindole **3** in 58% yield plus 15% of the diastereomeric oxindole **9**. A mechanism for this regioselective oxidation is proposed in Scheme 2. The *relative* configuration of the oxindole (**3**) is presumed to be that shown since, **2** displays complete facial selectivity in the oxidation to **4**; an x-ray crystal structure determination of **4** [5] suggests that the oxidation of **2** occurs from the least hindered face. Molecular models clearly show that the stereogenic center at C-10 mandates a conformation for **2** that folds one face of the indole toward the piperazinedione nucleus and severely limits access to that face. The exposed convex face of the indole is therefore, readily accessible to attack. These conformational considerations also apply to **2** and **7** which should be attacked by *tert*-butyl hypochlorite and subsequently, water, from the same (convex) face, ultimately producing **3**.[7,8] The incipient 3-chloroindolenines **7** (only the major isomer is shown; ~4 : 1 ratio) could be separated by chromatography or directly converted (crude) into **3** and **9** which were also readily separable.[8] Each diastereomeric 3-chloroindolenine (**7** and the C-3 epimer) suffered stereospecific conversion into **3** and **9**, respectively when treated with hot aqueous acetic acid.

In summary, the stereoselective cyclization furnishing **6** and the regio- and stereocontrolled conversion of **2** into either **3** or **4** by the simple alteration of oxidation reaction conditions provides a solid foundation from which to embrace the stereochemical and functional group complexities of **1**. It is also quite reasonable that a fused 2,3-disubstituted indole corresponding to **2** serves as a biosynthetic precursor to **1** by a similar regio- and stereoselective oxidation. Efforts to confirm this hypothesis as well as further synthetic studies toward **1** are in progress in these laboratories.

SCHEME 2



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References and Footnotes

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2. This substance is closely related to the marcfortines, obtained from cultures of *Penicillium roqueforti*: a) Polonsky, J.; Merrien, M.A.; Prange, T.; Pascard, C.; Moreau, S., *J. Chem. Soc. Chem. Comm.* (1980) 601, b) Prange, T.; Billion, M-A.; Vuilhorgne, M.; Pascard, C.; Polonsky, J., *Tetrahedron Lett.* (1981) **22**, 1977.
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4. European patent 301742A, Merck and Co. (July 28, 1987).
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6. Hollinshead, S.P.; Grubisha, D.S.; Bennett, D.W.; Cook, J.M., *Heterocycles* (1989) **29**, 529, and references cited therein.
7. Detailed experimental procedures and spetroscopic data for **2**,**4**,**5** and **6** have been previously reported.[5] Procedure for the oxidation of **2** to **3**: To a slution of **2** (70.0 mg, 0.150 mmol, 1.0 eq) and triethylamine (23 *u*L, 0.165 mmol, 1.1 eq) in dry methylene chloride (2 mL) cooled to 0° *t*-butyl hypochlorite (35.6 *u*L, 0.300 mmol, 2.0 eq) was aded in one portion. After 2 hrs at 0° TLC analysis indicates complete consumption of starting indole. The solvent was removed in vacuo and the oily residue was refluxed for 1 h with a 1:1 mixture of 10% aqueous acetic acid/methanol. The reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with water, dried over Na_2SO_4 and concentrated. The separation of the products on silica gel column (methylene chloride/acetone 10:1) furnished **3** (42 mg, 58%) and **9** (11 mg, 15%) both in the form of a colorless glass.

   3 ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 0.81 (3H, s); 0.84 (3H, s); 1.75 (1H, dd, J=12.7, 8.2 Hz); 1.84-1.94 (1H, m); 2.04-2.12 (3H, m); 2.42 (1H, 1/2 ABq, J=15.3 Hz); 2.87-2.95 (1H, m); 3.08 (1H, 1/2 ABq, J=15.3 Hz); 3.49-3.69 (3H, m); 3.72 (3H, s); 4.39 (1H, 1/2 ABq, J=16.2 Hz); 5.24 (1H, 1/2 ABq, J=16.2 Hz); 6.74-6.81 (3H, m); 6.94-6.99 (3H, m); 7.15-7.20 (1H, m); 7.32 (1H, d, J=6.8 Hz); 7.43 (1H, br. s).

   ^{13}C NMR (75.5 MHz, $CDCl_3$) δ $CDCl_3$: 19.8; 23.2; 24.8; 30.3; 30.5; 32.0; 44.1; 44.4; 46.0; 54.8; 55.2; 62.2; 67.9; 70.5; 109.1; 114.1; 122.1; 127.9; 128.3; 129.3; 130.0; 140.7; 158.7; 169.2; 172.7; 183.0.

   IR (NaCl, film): 3500; 3250; 1720; 1681; 1515; 1470; 1380; 1247 cm^{-1}. UV (MeOH) λ_{max} = 253; 277; 283 nm.
   High resolution mass spectrum : calcd. for $C_{29}H_{31}N_3O_4$: 485.23163. Found : 485.2319 .

   9 ^{1}H NMR (300 MHz, $CDCl_3$) δ TMS: 0.36 (3H, s); 0.96 (3H, s); 1.72-2.15 (5H, m); 2.35 (1H, 1/2 ABq, J=15.0 Hz); 2.47 (1H, dd, J=10.1, 7.8 Hz); 2.91 (1H, m); 3.43-3.51 (1H, m); 3.60 (1H, 1/2 ABq, J=15.0 Hz); 3.57-3.69 (1H, m); 3.80 (3H, s); 4.18 (1H, 1/2 ABq, J=15.5 Hz); 4.90 (1H, 1/2 ABq, J=15.5 Hz); 5.91 (1H, d, J=7.4 Hz); 6.56 (1H, t, J=7.4 Hz); 6.77-6.88 (3H, m); 7.06 (1H, t, J=7.5 Hz); 7.14 (2H, d, J=7.6 Hz); 8.18 (1H, s).

   ^{13}C NMR (75.5 MHz, $CDCl_3$) δ $CDCl_3$: 19.0; 23.7; 24.8; 30.0; 30.4; 31.1; 44.1; 46.2; 46.5; 55.3; 58.5; 61.9; 68.1; 70.5; 109.3; 114.5; 121.7; 123.7; 127.7; 129.1; 130.4; 134.6; 140.1; 159.2; 168.7; 173.1; 179.6.

   IR (NaCl, film): 3500; 3250; 1721; 1681; 1513; 1470; 1388; 1247 cm^{-1}.

   UV (MeOH) λ_{max}: 253; 277, 285 nm.
8. The relative stereochemical assignment for **3** and **9** was readily apparrent from the large relative upfield shifts (0.4 ppm and 0.9 ppm to 6.56 δ and 5.91 δ , respectively) of the proximal ortho indoxyl aromatic protons of **9** (relative to **3**) which are shielded by the *para*-methoxybenzyl group. In addition, there is a Δδ of 0.5 ppm upfield shift of one methyl group (to 0.35 δ) for **9** (relative to **3**) which is a result of the proximity of this methyl group to the indoxyl shielding cone of **3**. Extensive NOE experiments on each substance further corroborated these assignments.

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