Regioselective Amination of Indole-4,7-quinones

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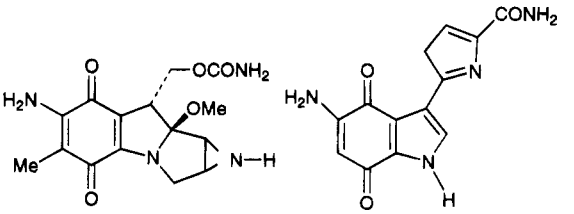
Amino derivatives of indole-4,7-quinones form the core of a large number of complex, biologically active natural products.[1] A few representative members of this class include the antitumor antibiotic mitomycin C (**1**),[2] the topoisomerase II inhibitor BE10988 (**2**),[3] and the marine alkaloids discorhabdin A (**3**)[4] and makaluvamine F (**4**).[5]

The direct amination of a *p*-quinone by ammonia or an amine is a well-known classical reaction. It involves an initial Michael addition of the amine to give, after rearomatization, an aminohydroquinone which is subsequently oxidized to an aminoquinone by excess quinone or an external oxidant.[6] We now report our results of a study of the reaction of the simple indole-4,7-quinone (**5**) and of its *N*-tosyl derivative **6** with the representative amine, benzylamine. Our objective was to compare the regioselectivity of amine addition in the two cases and to conclusively prove the structures of the products formed.

The synthesis of several reference aminoquinones of unambiguous structure was first carried out starting with *N*-tosyl-4,6,7-trimethoxyindole (**7**).[7] Oxidation of **7** by ceric ammonium nitrate (CAN) in a two-phase system afforded, in 75% yield, *N*-tosyl-6-methoxyindole-4,7-quinone (**8**); hydrolysis of **8** by sodium bicarbonate in aqueous methanol yielded (65%) 6-methoxyindole-4,7-quinone (**9**).[8] Treatment of **8** with benzylamine in refluxing benzene for 30 h resulted in the quantitative replacement of the 6-methoxyl substituent by the benzylamino group to yield the red aminoquinone **10**. Detosylation of **10** to 6-(benzylamino)indole-4,7-quinone (**11**) was achieved using sodium bicarbonate in aqueous methanol.



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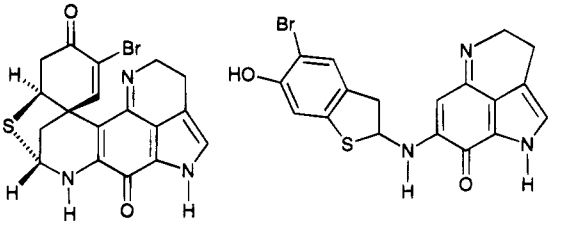

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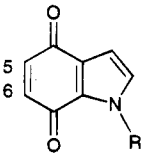
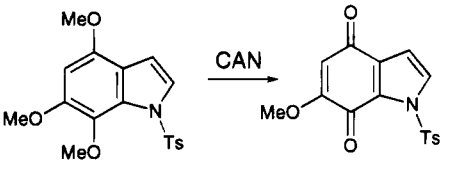
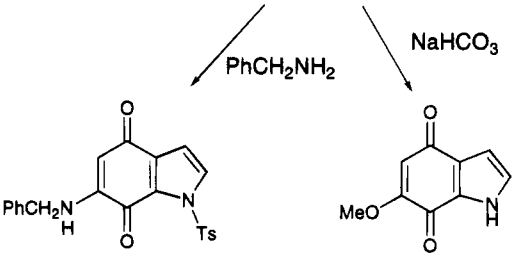


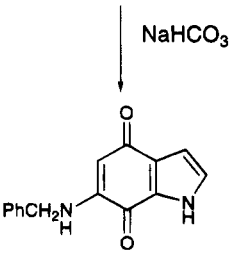
5, R = H
6, R = Ts



7 **8**



10 **9**



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The readily prepared 4,7-dimethoxyindole (**12**)[9] was converted to its *N*-tosyl derivative **13** by sodium hydride and *p*-toluenesulfonic anhydride, which gave a much

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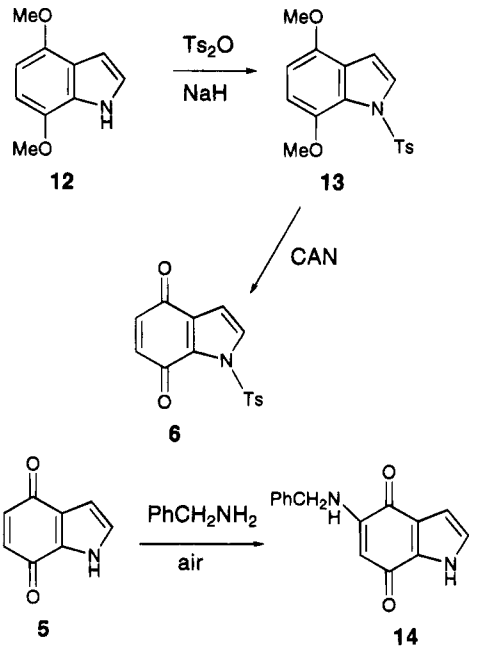
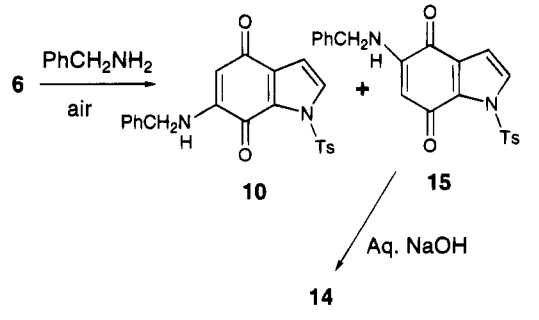
cleaner product than the more common reagent, tosyl chloride. Oxidation of **13** by CAN afforded, in good yield (73%), *N*-tosylindole-4,7-quinone (**6**). The unsubstituted 4,7-indolequinone (**5**) was prepared by the reported procedure which involves the CAN oxidation of *N*-carbomethoxy derivative of 4,7-dimethoxyindole followed by acid hydrolysis.[10] In contrast, we were unable to prepare **5** by alkaline hydrolysis of *N*-tosylquinone **6** or by CAN oxidation of the unprotected 4,7-dimethoxyindole (**12**).

Indole-4,7-quinone (**5**) reacted readily with benzylamine in the presence of air to give, in good yield, a single red quinone assigned the 5-benzylamino structure **14**; this assignment was secure since this product was isomeric with, but distinctly different from, the aminoquinone **11**.



In contrast, *N*-tosylindole-4,7-quinone (**6**) reacted with benzylamine in benzene to give a readily separable mixture of two red quinones (**10** and **15**) in a 3:1 ratio. The major product was identical to the 6-benzylamino isomer **10**, while mild basic hydrolysis of **15** afforded the detosylated quinone **14**.



In conclusion, the simple indole-4,7-quinone system, unsubstituted at both positions **5** and **6**, undergoes exclusive amination at position **5**, as expected electronically due to deactivation of the C-4 carbonyl by the indole nitrogen. In contrast, N-tosylation of the indole nitrogen not only largely cancels this effect, but leads to predominant amination at C-6. This observation is not only of some theoretical interest, but it also suggests potential utility for the synthesis of appropriate biologically significant indole derivatives.

Experimental Section

General. Melting points are uncorrected. Elemental analyses were performed by the Atlanta Microlab Inc., Atlanta, GA. All chromatography was carried out using silica columns.

***N*-(*p*-Toluenesulfonyl)-4,7-dimethoxyindole (13).** A solution of 4,7-dimethoxyindole **12** (2.0 g, 11.3 mmol) in anhydrous THF (55.0 mL) was added to a suspension of NaH (1.0 g, 41.7 mmol) in the same solvent (40.0 mL) maintained under nitrogen. The reaction mixture was stirred for 15 min after which a solution of *p*-toluenesulfonic anhydride (4.6 g, 14.1 mmol) in the same solvent (45.0 mL) was slowly added. The reaction mixture was further stirred for 3.0 h. Excess NaH was destroyed by slow addition of absolute ethanol. The solvent was then completely removed, and water (50.0 mL) was added to the residue. The residue was extracted with $CHCl_3$ (2 × 25 mL), and the organic extract was washed with water (3 × 50.0 mL) and dried (Na_2SO_4). Removal of solvent afforded the crude product which was purified by chromatography using hexanes/$CHCl_3$ 1:1 as eluent (3.7 g, 93%) mp 96–97 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.64 (s, 3H), 3.85 (s, 3H), 6.49 (d, 1H, J = 8.5 Hz), 6.58 (d, 1H, J = 8.7 Hz), 6.77 (d, 1H, J = 3.9 Hz), 7.23 (d, 2H, J = 8.2 Hz), 7.72 (d, 2H, J = 8.4 Hz), 7.76 (d, 1H, J = 3.8 Hz); *m/z* (relative intensity) 331 (M^+, 70.4), 222 (5.3), 176 (99.3), 162 (16.1), 148 (91.7), 133 (100.0), 117 (59.1). Anal. Calcd for $C_{17}H_{17}NO_4S$: C, 61.63; H, 5.14; N, 4.23. Found: C, 61.53; H, 5.18; N, 4.28.

***N*-(*p*-Toluenesulfonyl)indole-4,7-quinone (6).** A solution of CAN (5.0 g, 9.1 mmol) in water (10.0 mL) was added to a solution of **13** (1.0 g, 3.0 mmol) in acetonitrile (13.0 mL) and stirred for 1.0 h at rt. The organic and aqueous layers were separated. The aqueous layer was then extracted with $CHCl_3$ (3 × 20.0 mL). The organic extracts were combined and dried (Na_2SO_4). Removal of solvent gave the crude product as a yellow oil (1.0 g) which was purified by chromatography using hexanes/$CHCl_3$ 1:1 as eluent to afford **6** as a greenish yellow crystalline solid (0.66 g, 73%): mp 151–152 °C; ^1H NMR (360 MHz, CDC_{13}) δ 2.43 (s, 3H), 6.54 (d, 1H, J = 10.5 Hz), 6.60 (d, 1H, J = 10.5 Hz), 6.73 (d, 1H, J = 3.3 Hz), 7.35 (d, 2H, J = 8.0 Hz), 7.80 (d, 1H, J = 3.3 Hz), 8.04 (d, 2H, J = 8.0 Hz); *m/z* (relative intensity) 301 (M^+, 2.8), 237 (82.3), 222 (100.0), 208 (8.5), 180 (12.8), 155 (93.9), 147 (16.8), 120 (35.2). Anal. Calcd for $C_{15}H_{11}NO_4S$: C, 59.80; H, 3.66; N, 4.65. Found: C, 59.74; H, 3.72; N, 4.63.

***N*-(*p*-Toluenesulfonyl)-6-methoxyindole-4,7-quinone (8).** To a solution of **7** (0.40 g, 1.10 mmol) in CH_2Cl_2 (25.0 mL), tetrabutylammonium hydrogen sulfate (1.13 g, 3.33 mmol), and CAN (1.82 g, 3.32 mmol) were added under stirring. Water (20.0 mL) was added and the reaction mixture was stirred for 2.5 h at rt. The organic and aqueous layers were separated. The aqueous layer was then extracted with CH_2Cl_2 (3 × 30.0 mL). The organic extracts were then combined and dried (Na_2SO_4). Removal of the solvent gave the crude product which was purified by chromatography using CH_2Cl_2 as eluent to afford **8** as yellow crystals (0.28 g, 75%): mp 211–212 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 2.42 (s, 3H), 3.79 (s, 3H), 5.76 (s, 1H), 6.71 (d, 1H, J = 3.0 Hz), 7.34 (d, 2H, J = 8.0 Hz), 7.82 (d, 14, J = 3.0 Hz), 8.05 (d, 2H, J = 8.0 Hz); *m/z* (relative intensity) 331 (M^+, 1.0), 176 (34.6), 155 (19.9), 120 (20.7), 91 (100.0), 65 (26.4); HRMS calcd for $C_{16}H_{13}NO_5S$ 331.051445, found 331.052994.

6-Methoxyindole-4,7-quinone (9). To a saturated solution of $NaHCO_3$ (8.0 mL) was added a solution of **8** (0.24 g, 0.73 mmol) in methanol (20.0 mL), and the reaction mixture was refluxed for 35 min. The solvent was removed, and water (100.0 mL) was added to the residue. This was then extracted with $CHCl_3$ (5 × 50.0 mL) and dried (Na_2SO_4). Removal of solvent gave the crude product, which was purified by chromatography using $CHCl_3$/ethyl acetate 5:1 as eluent to obtain **9** as orange crystals (0.08 g, 65%): mp 288–289 °C dec [lit.[8] 210–212 °C dec]; ^1H NMR (360 MHz, DMSO-d_6) δ 3.76 (s, 3H), 5.80 (s, 1H),

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6.47 (s, 1H), 7.25 (s, 1H), 8.40 (bs, 1H); *m/z* (relative intensity) 177 (M^+, 72.0), 162 (8.7), 148 (31.7), 134 (15.2), 120 (100.0). Anal. Calcd for $C_9H_7NO_3$: C, 61.02; H, 3.96; N, 7.91. Found: C, 60.94; H, 4.02; N, 7.83.

6-(*N'*-Benzylamino-*N*-(*p*-toluenesulfonyl)indole-4,7-quinone (10). Benzylamine (3 drops) was added to a solution of **8** (0.025 g, 0.08 mmol) in benzene (5.0 mL), and the reaction mixture was refluxed for 30 h. The color of the reaction mixture turns from yellow to deep red. Removal of solvent gave the crude product, which was purified by chromatography using $CHCl_3$ as eluent to afford **10** as red crystals (0.031 g, 100%): mp 175–176 °C; ^1H NMR (360 MHz, $CDCl_3$) δ 2.43 (s, 3H), 4.23 (d, 2H, J = 5.6 Hz), 5.34 (s, 1H), 6.07 (bt, 1H), 6.71 (d, 1H, J = 3.0 Hz), 7.23–7.36 (m, 7H), 7.79 (d, 1H, J = 3.0 Hz), 7.98 (d, 2H, J = 8.0 Hz); *m/z* (relative intensity) 46 (M^+, 6.6), 250 (85.6), 235 (24.7), 181 (5.1), 162 (10.1), 149 (34.5), 136 (32.9), 129 (100.0). Anal. Calcd for $C_{22}H_{18}N_2O_4S$: C, 65.03;, H, 4.43; N, 6.90. Found: C, 64.99; H, 4.51; N, 6.85.

Amination of 6. Benzylamine (0.12 mL, 1.70 mmol) was added to a solution of **6** (0.17 g, 0.56 mmol) in benzene (5.0 mL), and the reaction mixture was stirred for 1.0 h at rt. The color of the reaction mixture turns from yellow to deep red. Removal of solvent gave a residue which was purified by chromatography, using $CHCl_3$ as eluent, to obtain two products, **10** (0.16 g, 68%) as red crystals and **15** as a red foamy solid (0.05 g, 22%).

Compound 15: ^1H NMR (360 MHz, $CDCl_3$) δ 2.41 (s, 3H), 4.25 (d, 2H, J = 6.0 Hz), 5.20 (s, 1H), 6.02 (bt, 1H), 6.67 (d, 1H, J = 3.0 Hz), 7.22–7.35 (m, 7H), 7.68 (d, 1H, J = 3.0 Hz), 8.00 (d, 2H, J = 8.0 Hz); *m/z* (relative intensity) 406 (M^+, 3.3), 342 (39.2), 325 (19.0), 252 (100.0), 235 (27.3), 223 (11.3), 195 (5.0), 120 (7.7), 106 (30.3); HRMS calcd for $C_{22}H_{18}N_2O_4S$ 406.098729, found 406.098068.

6-(*N'*-Benzylamino)-indole-4,7-quinone (11). Method 1. An aqueous solution of NaOH (1.0 M) was added dropwise to a solution of **10** (0.02 g, 0.05 mmol) in methanol (5.0 mL) until the color of the reaction mixture turned from red to dark brown. Approximately 4 drops was required. The reaction mixture was stirred for 5.0 min and then neutralized with aqueous HCl (10% solution, 3 drops). The solvent was then removed, and the residue was extracted with $CHCl_3$(15.0 mL). The organic extract was washed with water (3 × 5.0 mL) and dried (Na_2SO_4). Removal of the solvent and purification of the crude product by chromatography using $CHCl_3$/ethyl acetate 4:1 afforded **11** (0.01 g, 80%): mp 218–220 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 4.35 (d, 2H, J = 6.35 Hz), 4.99 (s, 1H), 6.35 (d, 1H, J = 1.66 Hz), 7.28 (m, 5H), 7.78 (t, 1H, J = 6.30 Hz), 8.48 (bs, 1H); *m/z* (relative intensity) 252 (M^+, 100.0), 235 (91.4), 223 (10.0), 195 (8.5), 175 (8.1), 161 (7.7), 147 (8.0), 136 (17.4), 120 (49.5); HRMS calcd for $C_{15}H_{12}N_2O_2$ 252.089878, found 252.089271.

Method 2. Benzylamine (0.04 mL, 0.37 mmol) was added to a dispersion of **9** (0.02 g, 0.05 mmol) in methanol (5.0 mL), and the reaction mixture was refluxed for 72.0 h. The residue, obtained after the removal of solvent, was extracted with $CHCl_3$ (25.0 mL). The organic extract was washed with water (3 × 50.0 mL) and dried (Na_2SO_4). Removal of the solvent and purification of the crude product by chromatography using $CHCl_3$/ethyl acetate 4:1 afforded **11** (0.01 g, 35%).

5-(*N'*-Benzylamino)indole-4,7-quinone (14). Method 1. An aqueous solution of NaOH (1.0 M) was added dropwise (4 drops) to a solution of **15** (0.02 g, 0.05 mmol) in methanol (5.0 mL) until the color changed to dark brown. After 5.0 min, the reaction mixture was neutralized with aqueous HCl (10% solution, 3 drops). The solvent was removed, and the residue was extracted with $CHCl_3$(15.0 mL). The organic extract was washed with water and dried (Na_2SO_4). Removal of the solvent and purification of the crude product by chromatography using $CHCl_3$/ethyl acetate 4:1 as eluent gave **14** (0.01 g, 79%): mp 248–249 °C; ^1H NMR (360 MHz, DMSO-d_6) δ 4.36 (d, 2H, J = 6.0 Hz), 4.99 (s, 1H), 6.47 (d, 1H, J = 3.0 Hz), 6.97 (d, 1H, J = 3.0 Hz), 7.22–7.35 (m, 5H), 7.96 (bt, 1H), 8.80 (bs, 1H); *m/z* (relative intensity) 252 (M^+, 100.0), 235 (34.1), 195 (10.8), 161 (9.9), 149 (14.1), 132 (42.5), 120 (29.5); HRMS calcd for $C_{15}H_{12}N_2O_2$ 252.089878, found 252.088670.

Method 2. Benzylamine (1 drop) was added to a solution of **5** (0.01 g, 0.07 mmol) in benzene (2.0 mL), and the reaction mixture was refluxed for 1.25 h. The solvent was removed, and the residue was purified by chromatography using $CHCl_3$/ethyl acetate 4:1 as eluent to afford **14** (0.012 g, 71%).

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