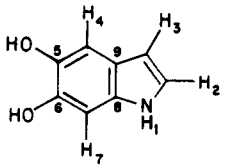
Table I. A Summary of NMR Chemical Shifts of 5,6-Dihydroxyindole



	H or C	ppm
^1H ($CDCl_3$)[a]	H_2	6.20 (d, J = 8.02 Hz)
	H_3	6.98 (d, J = 8.02 Hz)
	H_4	6.89 (s)
	H_7	6.82 (s)
^{13}C ($CDCl_3$)[a]	C_2	122.77
	C_3	101.31
	C_4	104.87
	C_5	130.65
	C_6	140.55
	C_7	98.66
	C_8	142.35
	C_9	120.96

[a] Relative to external Me_4Si.

1-methylindole[7] has ionization constants of 8.4 and 10.7 in water. Additionally, *m*- and *p*-aminophenols have pK_a's of 9.9 and 8.3, respectively.[8] This suggests that the second pK_a of **2**, which is greater than 10.2, may be ascribed to the 6-hydroxyl group.

The FT-IR spectrum was consistent with those for O–H, C–O, C–N, aromatic C–H, and N–H bonds of hydroxylated indoles, and the spectrum compares well with that for 5-hydroxyindole.[9,10]

The EI quadrapole mass spectrum has a molecular ion with *m/e* 149. The fragmentation pattern showed the loss of H_2O (*m/e* 131), HCN (*m/e* 120), and H_2O/CO (*m/e* 103), was consistent with that reported for indoles.[11]

The 300-MHz ^1H NMR showed two doublets and two singlets. Irradiation of the doublet at 6.20 ppm (J = 8.2 Hz) caused the doublet at 6.98 ppm to collapse to a singlet. The downfield signal was assigned to H-2 and the latter to H-3. Additionally, the broadened singlet at 6.89 ppm sharpened upon irradiation of the 6.98 ppm doublet, which showed this to be the H-3/H-4 pair. These data are summarized in Table I.

^{13}C NMR spectra were recorded at 75.48 MHz. Proton decoupled experiments gave spectra with eight resonance signals. The single frequency off-resonance-decoupled spectrum showed that the signals at 122.77, 101.31, 104.87, and 98.66 were sp^2 carbons singly bonded to hydrogen. Carbons 5 and 6 were distinguished by additivity rules.[12] The assignments for C-8 and C-9 were made based on comparison with known substituted indoles, and T_1 inversion-recovery experiments supported these assignments[13] (Table I).

Experimental Section

Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H NMR and ^{13}C NMR spectra were obtained on a General Electric QE-300 (at 300 MHz and 75.48 MHz, respectively) NMR spectrometer, and chemical shifts are recorded relative to external tetramethylsilane. Mass spectra were obtained on a Finnegan 4000 GC/MS/DS system. A Nicolet FX-5 FT-IR infrared spectrophotometer was used to obtain IR spectra of **2** as KBr pellets. HPLC analyses were performed on a Hi-bar LiChrosorb RP-18 (10 μm) column (E. Merck), with detection at 290 nm by a Waters Associates Lambda Max variable-wavelength detector. UV–visible spectra were obtained on a Perkin-Elmer 553 B UV–visible spectrophotometer.

The method of Albert and Sargent[14] was used to determine pK_a values. The pH of an anaerobic solution of the indole in a UV cuvette was raised incrementally with 1 N NaOH, and the UV–visible spectrum was recorded.

4,5-Dihydroxy-2,β-dinitrostyrene (**3**) was synthesized from 3,4-bis(benzyloxy)benzaldehyde (Aldrich) by the method of Murphy and Banks.[4]

5,6-Dihydroxyindole (2). A mixture of 100 mg (0.44 mmol) of 4,5-dihydroxy-2,β-dinitrostyrene (**3**), 25 mL of CH_3OH, and 20 mg of 10% Pd/C was hydrogenated in a Parr apparatus at 50 psi of H_2 for 1 h. The solvent was removed in vacuo, and the resulting solid sonicated in dry CH_2Cl_2. The mixture was filtered and filtrate concentrated in vacuo and chromatographed (60–200 mesh silica gel) with 1:1 diethyl ether/dichloromethane to yield 35–50 mg (53–76%) of nearly colorless crystals: mp 141–142 °C (lit.[2] 141 °C). HPLC analysis of the sample (0.5 mL/min flow rate) gave the retention times for **2** of 10.1 min with 50% aqueous methanol as the mobile phase and 8.6 min with 40% aqueous acetonitrile.

Registry No. **2**, 3131-52-0; **3**, 96806-57-4; MeOH, 67-56-1; Pd, 7440-05-3; H_2, 1333-74-0.

(7) The sample of 5,6-dihydroxy-1-methylindole was a generous gift from Dr. G. Prota, University of Naples, Naples, Italy.

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(13) Carbon 8, which is bonded to the electron-rich nitrogen, had the expected[12] shorter inversion time (99 ± 4 s vs. 129 ± 4 s).

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Benzylic Oxidation Using *tert*-Butyl Hydroperoxide in the Presence of Chromium Hexacarbonyl

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Oxidation of tetralin derivatives to their corresponding α-tetralones is of considerable value in organic synthesis, and many methods have been reported for accomplishing this conversion.[1,2] Such benzylic oxidations are traditionally performed with chromic acid and have been applied to the conversion of estrones to their 6-oxo derivatives, which are of potential value in the preparation of steroid–protein conjugates useful for radioimmunoassay purposes.[3] However, low yields (1–43%) are reported for this reaction, due to a number of side products being formed by cleavage of the B and C rings.[1] Alternative

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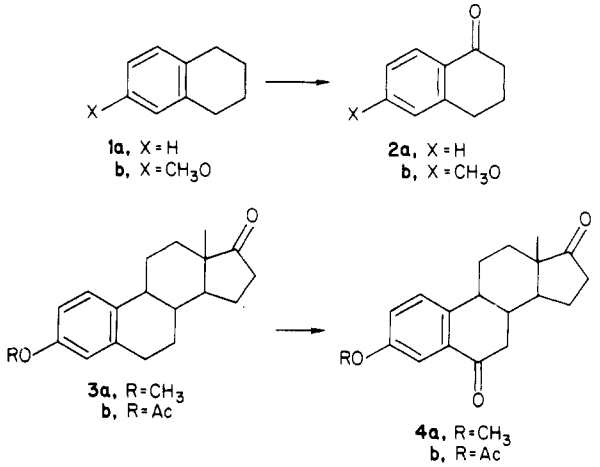
Table I. Benzylic Oxidations Using *t*-BuOOH/Cr(CO)$_6$

starting material	product	conversn, %	yield,[a] %
tetralin	α-tetralone	100	88
6-methoxytetralin	6-methoxy-α-tetralone	72	61
3a	**4a**	63	85
3b	**4b**	52	54

[a] Based on starting material consumed.

procedures,[2] even microbiological hydroxylation,[2a] have not led to convenient high yield benzylic oxidations.

We recently observed that oxidation of cycloalkenes to α,β-unsaturated ketones could be effected by *tert*-butyl hydroperoxide in the presence of chromium hexacarbonyl catalyst,[4] and we now report the use of this system for benzylic oxidation. Using this procedure, tetralin (**1a**) was



converted to α-tetralone (**2a**), 6-methoxytetralin (**1b**) to 6-methoxy-α-tetralone (**2b**), 3-methoxyestra-1,3,5(10)-trien-17-one (**3a**) to 6-oxoestrone 3-methyl ether (**4a**), and 3-acetoxyestra-1,3,5(10)-trien-17-one acetate (**3b**) to its 6-oxo derivative **4b**. The yields are summarized in Table I. While the oxidation of tetralin proceeded to completion and gave high yield of tetralone, we were unable to drive the other reactions to completion, but starting materials were easily separated, allowing isolation of pure ketones. In all cases, the yields were far superior to those obtained by chromic acid oxidation.[1]

Of particular interest is the fact that these oxidations appear to involve catalysis by Cr(0) species. While the mechanism is not yet established, it is noteworthy that the reaction medium remains almost colorless throughout, while admixture of *t*-BuOOH and chromium oxides in acetonitrile leads to deep red solutions.[5] We anticipate studying the mechanism of this interesting reaction in the near future.

Experimental Section

Infrared spectra were determined on a Perkin-Elmer 1420 spectrometer, NMR spectra on Varian XL200 spectrometer, and melting points were determined on a Fisher Johns apparatus and are uncorrected. Chromium hexacarbonyl was purchased from Strem Chemicals, and *tert*-butyl hydroperoxide (90% solution containing 5% H_2O, 5% *tert*-butyl alcohol) was purchased from Aldrich Chemical Company. Acetonitrile was distilled prior to use. All reactions were run under an atmosphere of nitrogen. (*CAUTION*: *tert*-butyl hydroperoxide may present an explosion hazard when concentrated. It is recommended that large-scale reactions be worked up using aqueous sodium metabisulfite).

Oxidation of Tetralin. To a solution of tetralin (500 mg, 3.78 mmol) in acetonitrile (25 mL) was added *tert*-butyl hydroperoxide (1.14 mL, 11.40 mmol) and chromium hexacarbonyl (250 mg, 1.14 mmol). The mixture was boiled under reflux for 23 h and then cooled to room temperature. Water (100 mL) was added and the product was extracted with ether (3 × 20 mL). The extracts were washed with water, aqueous sodium hydrogen carbonate, and brine, dried ($MgSO_4$), and evaporated to give the crude product. Purification by flash chromatography afforded pure α-tetralone (489 mg, 88%) spectroscopically identical with an authentic sample.

Oxidation of 6-Methoxytetralin. 6-Methoxytetralin (255 mg, 1.57 mmol) with *tert*-butyl hydroperoxide (0.57 ml) and chromium hexacarbonyl (124 mg, 0.56 mmol) were treated as above. Flash chromatography afforded unreacted starting material (71 mg) and 6-methoxy-α-tetralone (122 mg, 61% based on starting material consumed), identical with an authentic sample.

Oxidation of 3-Methoxyestra-1,3,5(10)-trien-17-one. Estrone 3-methyl ether (300 mg, 1.05 mmol) was treated with *tert*-butyl hydroperoxide (0.32 mL, 3.18 mmol) and chromium hexacarbonyl (69 mg, 0.31 mmol) as above (reflux, 29 h). Flash chromatography gave unreacted starting material (110 mg) and 3-methoxyestra-1,3,5(10)-triene-6,17-dione (**4a**) (169 mg, 85% based on starting material consumed): Mp 144–145 °C (lit.[1] mp 144–145 °C; IR ($CHCl_3$) ν_{max} 1740, 1685 cm^{-1}; NMR ($CDCl_3$, 200 MHz) δ 7.58 (1 H, d, J = 2.9 Hz), 7.35 (1 H, d, J = 8.4 Hz), 7.13 (1 H, dd, J = 8.4, 2.9 Hz), 3.86 (3 H, s), 2.88 (1 H, dd, J = 16.5, 3 Hz), 0.93 (3 H, s), 2.6–1.1 (methylenes, etc.).

Oxidation of 3-Acetoxyestra-1,3,5(10)-trien-17-one. Estrone acetate (100 mg, 0.32 mmol) was treated with *tert*-butyl hydroperoxide (0.10 mL, 1.0 mmol) and chromium hexacarbonyl (21 mg, 0.09 mmol) as described above (reflux 24 h). Purification by preparative TLC afforded unreacted starting material (48 mg) and 3-acetoxyestra-1,3,5(10)-triene-6,17-dione (**4b**) (29 mg, 54% based on starting material consumed): IR ($CHCl_3$) ν_{max} 1765, 1740, 1687, 1613 cm^{-1}; NMR (200 MHz, $CDCl_3$) δ 7.77 (1 H, d, J = 2.5 Hz), 7.46 (1 H, d, J = 8 Hz), 7.28 (1 H, dd, J = 8, 2.5 Hz), 2.88 (1 H, dd, J = 16.5, 3.5 Hz), 2.32 (3 H, s), 0.92 (3 H, s), 2.6–1.1 (methylenes, etc.).

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Registry No. **1a**, 119-64-2; **1b**, 1730-48-9; **2a**, 529-34-0; **2b**, 1078-19-9; **3a**, 1624-62-0; **3b**, 901-93-9; **4a**, 19115-79-8; **4b**, 7323-89-9; *t*-BuOOH, 75-91-2; $Cr(CO)_6$, 13007-92-6.

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(5) During attempts to modify and optimize this procedure, we have found that $Cr(CO)_5(CH_3CN)$ reacts instantly with *t*-BuOOH to give a brown material, presumably an oxide of chromium. Use of this mixture does lead to benzylic oxidation, but several other products are also obtained. This is in contrast to $Cr(CO)_6$ which does not give any colored substances even on prolonged heating with *t*-BuOOH in acetonitrile.

A Convenient Method for the Preparation of N-Blocked Amino Acids

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Carbamates have been used to protect the amino function of α-amino acids since Bergmann and Zervas[1] first investigated the use of the benzyloxycarbonyl (Cbz) group in 1932. These groups are most commonly introduced by

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