Some Observations on the Formation of 1-Hydroxyindoles in the Leimgruber-Batcho Indole Synthesis [1]

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The factors influencing the formation of 1-hydroxyindoles in the catalytic hydrogenation of β-dimethylamino-2-nitrostyrenes (Leimgruber-Batcho indole synthesis) have been investigated. Significant amounts of 1-hydroxyindoles were obtained only when the β-dimethylamino-2-nitrostyrene was substituted with an electron-withdrawing group at the 5 or 6 position. The proportion of 1-hydroxyindole formed relative to the normal indole product was found to increase as both the amount of catalyst and hydrogen pressure were decreased.

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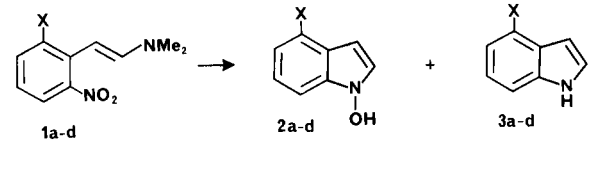
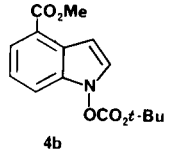
Somei [2] recently reported the formation of the relatively stable 1-hydroxyindoles **2a,b** and the unstable **2c** by reduction of the *trans*-β-dimethylamino-2-nitrostyrenes **1a-c** with either titanium(III) chloride or zinc in aqueous ammonium chloride (Scheme 1). Compounds **2a** and **2b** are the first examples of stable 4-substituted 1-hydroxyindoles. The only other examples of stable 1-hydroxyindoles are those which are substituted with electron withdrawing groups in the five-membered ring or a bulky group at the 2-position [3,4]. Our observation of the formation of 1-hydroxyindoles **2b** and **2d** by catalytic hydrogenation of **1b** and **1d** during the Leimgruber-Batcho indole synthesis [5] of **3b** and **3d** prompted us to undertake a study to define conditions conducive to the formation of either 1-hydroxyindoles or indoles by catalytic hydrogenation. Furthermore, it was of interest to study other positional isomers of **1** to determine the factors which influence the formation (and stability) of 1-hydroxyindoles in the Leimgruber-Batcho indole synthesis.

Kozikowski reported that hydrogenation of **1b** (7.0 g) in benzene (140 ml) with 10% palladium on carbon (1.4 g) gave an 82% yield of **3b** [6]. Although we were able to reproduce this on a similar scale, attempts to scale this reaction up led to the formation of considerable amounts of the 1-hydroxyindole **2b** at the expense of **3b**. A change in solvent from benzene to tetrahydrofuran was made, since large-scale reductions in benzene proved to be extremely sluggish (incomplete reaction after 24 hours) due to the separation of water from the mixture which caused adhesion of the catalyst to the reaction vessel wall. In tetrahydrofuran the reductions were exothermic and uptake of hydrogen ceased in less than one hour. The results of several of these reductions under varying conditions are presented in Table I. Compound **2b**, although relatively stable at

Scheme 1



a: X= NO_2
b: X= CO_2Me
c: X= OCH_2Ph
d: X= CN



4b

Table I

Catalytic Hydrogenation of **1b** [a]

Entry	Grams **1b**	Grams 10% Pd-C	Ratio **1b**/Catalyst	Solvent (ml)	Yield (%) [b] **2b**	Yield (%) [b] **3b**
1	3.6	0.75	4.8	C_6H_6 (140)	<5 [c]	81
2	7.0	1.4	5.0	C_6H_6 (140)	14	57
3	7.0	1.0	7.0	THF (140)	33 [d]	41
4	50	2.0	25	THF (300)	>50 [c]	24
5	80	1.5	53	THF (750)	>60 [c,e]	<10

[a] Hydrogenations were carried out on a Parr apparatus at an initial pressure of 50 psi until uptake of hydrogen ceased. [b] Isolated by silica gel chromatography unless otherwise indicated. [c] Estimated by tlc analysis of reaction mixture. [d] Yield of the *t*-BOC derivative **4b**. [e] Subsequent reduction with zinc-acetic acid gave 65% of **3b**.

Table II

Catalytic Hydrogenation of **1d** [a]

Entry	Grams **1d**	Grams 10% Pd-C	Ratio **1d**/Catalyst	Solvent (ml)	Yield (%) [b] **2d**	**3d**
1 [c]	10.8	2.7	4.0	CH_3OH (250)	14	70
2	3.5	0.75	4.7	CH_3OH (140)	7	69
3 [d]	3.5	0.75	4.7	CH_3OH (140)	54	35
4	3.5	0.75	4.7	C_6H_6 (140)	33	50
5	3.5	0.75	4.7	THF (140)	26	53
6	50	2.0	25	THF (350)	54	36
7	3.5	0.10	35	THF (140)	56	22
8 [e]	3.5	0.075	75	THF (140)	75	17

[a] See Table I, note [a]. [b] Yield of isolated product (silica gel chromatography). [c] Hydrogenation at 60 psi. [d] Hydrogenation at atmospheric pressure for 24 hours. [e] Hydrogenation for 12 hours.

room temperature, was unstable to silica gel chromatography, and therefore the yields of this compound in most cases could only be estimated by the analysis of the reaction mixture or by subsequent conversions (acylation to **4b** or zinc-acetic acid reduction to **3b** [7]. It is clear from the data in Table I that the yield of **3b** increased as the ratio of starting material **1b** to catalyst was increased.

Similar results were obtained in the reduction of nitrile **1d** (Table II). The highest yield of indole **3d** (70%) was obtained by conducting the hydrogenation in methanol at 60 psi using a heavy catalyst load (entry 1). Methanol proved to be superior to tetrahydrofuran for optimization of the yield of **1d**. As the amount of catalyst was decreased, the yield of the 1-hydroxyindole **2d** increased, and a yield of **2d** of 75% was realized (entry 8).

Scheme 2

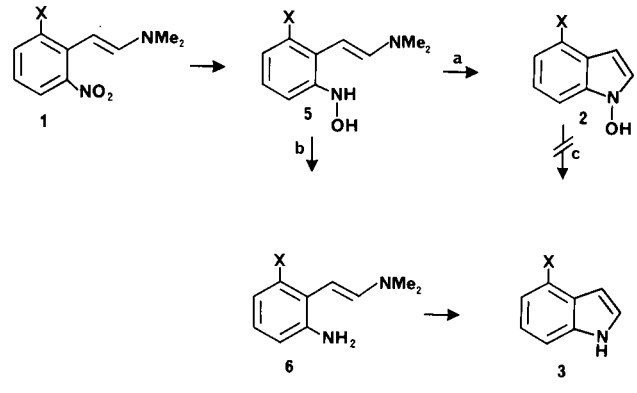
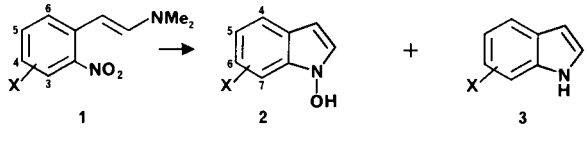


Table III

Catalytic Hydrogenation of Substituted *trans*-β-Dimethylamino-2-nitrostyrenes [a]



Entry	X	Yield (%) [b]	Mp, °C (lit mp, ref)	Yield (%) [b]	Mp, °C (lit mp, ref)
d	6-CN	26	126-128	53	119-120 (120-121, [12])
e	5-CN	29	83-84	44	104-105 (104-106, [13])
f	4-CN	4	109-110	86	126-128 (129-130, [14])
g	3-CN	0		44	95-96 (96, [15])
h	3-CO_2CH_3	0		61	44-45 ([16])
i	5-F	<5 [c]		55	44-45 (46-47, [5])
j	4-F	<5 [c]		35	73-74 (74-75, [5])
k	6-OCH_3	0		70	67-68 (69.5, [17])
l	6-NO_2	27	159-160 (154-156, [2])	9	195-196 (206-207, [2])
m	6-CH_3	0		60	oil

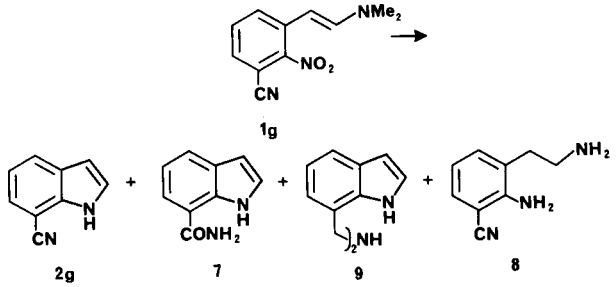
[a] Hydrogenation of 3.5 g of **1** with 0.75 g 10% Pd-C in 140 ml of tetrahydrofuran for ≅1 hour. [b] Isolated by silica gel chromatography unless otherwise indicated. [c] Estimated by tlc, unstable to isolation.

Compound **2d** is a stable, crystalline material which, unlike **2b** survived silica gel chromatography. No significant decomposition was noted after storage at room temperature for several months. A mechanistic rationale for these results is presented in Scheme 2. The rate of formation of the indole product **3** is dependent on the rate of reduction of the hydroxylamine intermediate **5** to the aniline **6** (step b). The rate of step b is clearly dependent on the amount of catalyst. The alternative pathway for **5** (step a) is simply ring closure to the 1-hydroxyindole **2**. Hence, it is reasonable that decreasing the amount of catalyst funnels intermediate **5** into the pathway leading to **2** at the expense of **3**. The effect of decreasing the hydrogen pressure, which also slows step b, can be seen by comparing entries 2 and 3 in Table II. The yield of **2d** increased from 7% to 54%, as the pressure was decreased from 50 psi to atmospheric. An alternative explanation for these results would be that the 1-hydroxy group of **2** is reduced to give **3** (step c). However, we discount this pathway since, in all cases examined (with the exception of the atmospheric reduction), there was an abrupt cessation of hydrogenation uptake after which time no further change in product distribution (tlc analysis) was noted. Thus, the 1-hydroxyindoles appear to be stable to catalytic hydrogenation.

The yields of indole **3** and 1-hydroxyindole **2** products from various substituted positional isomers of **1** obtained under identical reaction conditions are presented in Table III. The results indicate that substantial quantities of 1-hydroxyindoles were obtained only when **1** was substituted at position 5 or 6 with an electron-withdrawing group (CN, NO_2). Of the three 1-hydroxycyanoindole isomers isolated, the order of stability was 4-CN $\gg$ 5 CN $\approx$ 6CN. The latter two crystalline compounds were stable when refrigerated (−20°) in the dark but decomposed at room temperature to highly colored by-products.

Table IV

Catalytic Hydrogenation of **1g** [a]



Solvent	Yield (%) [b]			
THF	44	0	8	40
C_6H_6	26	44	0	<5
CH_3OH	37	29	0	<10

[a] Conditions were as described in Table III. [b] Yield of isolated material, see experimental section.

The 3-CN isomer **1g** gave different products depending upon the solvent used in the reaction (Table IV). The formation of benzamides in the reduction of *o*-cyanonitrobenzenes is well-precedented [9] and hence, production of 7-carboxamidoindole (**7**) is easily explained. The formation of **9** probably involves reductive amine-imine coupling [10].

In conclusion, the formation of 1-hydroxyindoles in the Leimgruber-Batcho indole synthesis using catalytic hydrogenation occurs to a significant extent only when the β-dimethylamino-2-nitrostyrene (**1**) is substituted with a strongly electron-withdrawing group at the 5 or 6 position (NO_2, CN, CO_2CH_3) [11]. The ratio of 1-hydroxyindole to indole formed is dependent both on the amount of catalyst used and on the hydrogen pressure with a small amount of catalyst and low pressure favoring formation of 1-hydroxyindole. The 1-hydroxyindoles substituted at the indole 4 position with carbomethoxy, cyano, or nitro are remarkably stable considering the instability of the unsubstituted parent [4]. For certain synthetic applications, the formation of 1-hydroxyindoles is irrelevant. For example, the synthesis of indole-4-carboxaldehyde (**10**) is more expeditiously carried out by reduction of the mixture of **2d** and **3d** (obtained from hydrogenation) with Raney nickel-sodium hypophosphite.

EXPERIMENTAL

Proton magnetic resonance spectra were recorded with Varian A-60 and Bruker WM 300 instruments and are reported in ppm δ downfield from an internal standard of tetramethylsilane. Mass spectra were obtained in either an Atlaswerke CH-4 or CH-7 instrument. Microanalyses were performed by Syntex Analytical Department. Reactions were monitored by thin layer chromatography on 250 μ layers of silica gel GF on glass plates. Silica gel column chromatography was performed using 70-230 mesh (Merck) silica gel. Melting points are uncorrected. The ir spectra were measured with a Perkin-Elmer Model 237 grating infrared spectrophotometer.

trans-β-Dimethylamino-2-nitrostyrenes **1a-m**.

These compounds were prepared from the requisite nitrotoluene by heating in dimethylformamide with *N,N*-dimethylformamide dimethyl acetal as has been previously described [2,5,6,8]. The crude products thus obtained were > 95% pure by nmr analysis and were not further purified.

Methyl Indole-4-carboxylate (**3b**), Methyl-1-(*t*-butoxycarbonyl)indole-4-carboxylate (**4b**), and Methyl-1-hydroxyindole-4-carboxylate (**2b**).

Table I, Entry 3.

A mixture of 7.0 g (28 mmoles) of 6-methoxycarbonyl-*trans*-β-dimethylamine-2-nitrostyrene (**1b**) [6] and 1.0 g of 10% palladium on carbon in 140 ml of tetrahydrofuran was shaken in a Parr apparatus at an initial hydrogen pressure of 50 psi for 12 hours. Uptake of hydrogen was complete within 90 minutes. The mixture was filtered and evaporated *in vacuo*, and the residue was partitioned between ether and 5% hydrochloric acid. The ether solution was washed with brine, dried over sodium sulfate, and evaporated to a residue which was taken up in 75 ml of tetrahydrofuran. Di-*t*-butyl dicarbonate (96 g, 27.5 mmoles) and 0.25 g of potassium *t*-butoxide were added, and the resulting solution was heated at reflux for 10 minutes. The tlc analysis (silica gel, 1% methanol-chloro-

form) showed conversion of the 1-hydroxyindole **2b** (rf 0.16) to the *t*-BOC derivative **4b** (rf 0.70), while the indole **3b** (rf 0.42) was unchanged. The mixture was added to water, extracted with ether, and the ether extract was washed with brine, dried over sodium sulfate, and evaporated *in vacuo*. Chromatography of the residue on silica gel (40% ether-hexanes) gave 2.7 g of **4b** (33%) and 2.0 g of **3b** (41%). Compound **4b** had mp 86-87°; ir (potassium bromide): 1790, 1705, 1260, 1240, 1140 cm^{-1}; nmr (deuteriochloroform): δ 1.56 (s, 9H), 3.96 (s, 3H), 7.10 (d, 1H, J = 3.7 Hz), 7.30 (dd, 1H, J = 8.0, 8.0 Hz), 7.34 (d, 1H, J = 3.7 Hz), 7.48 (d, 1H, J = 8.0 Hz), 7.92 (d, 1H, J = 8.0 Hz).

Anal. Calcd. for $C_{15}H_{17}NO_5$ (291.30): C, 61.85; H, 5.88; N, 4.81. Found: C, 61.99; H, 5.90; N, 4.79.

Compound **3b** had mp 63-64° (lit [6] mp 63°).

Table I, Entry 5.

A mixture of 80 g (320 mmoles) of **1b** and 1.5 g of 10% palladium on carbon in 750 ml of tetrahydrofuran was hydrogented for 12 hours on a Parr apparatus at 50 psi. The reaction mixture was processed as before to give a semi-solid residue which by tlc analysis appeared to be ≈ 90% compound **2b** with the remainder **3b**. Trituration of a small sample with dichloromethane gave pure **2b** which was recrystallized from methanol-water. Compound **2b** had mp 112-113°; ir (potassium bromide): 3600-3200, 1695, 1300, 1275 cm^{-1}; nmr (acetone-d_6): δ 3.93 (s, 3H), 6.92 (dd, 1H, J = 3.3, 0.8 Hz), 7.27 (dd, 1H, J = 8.0, 8.0 Hz), 7.53 (d, 1H, J = 3.3 Hz), 7.71 (ddd, 1H, J = 8.0, 1.0, 0.8 Hz, C_7H), 7.82 (dd, 1H, J = 8.0, 1.0 Hz, C_5H); ms: m/e 191 (M^+), 175, 160, 144, 132.

Anal. Calcd. for $C_{10}H_9NO_3$ (191.18): C, 62.83; H, 4.74; N, 7.32. Found: C, 63.06; H, 4.81; N, 7.37.

The crude product from above was dissolved in 250 ml of acetic acid, 30 g (460 mmoles) of zinc dust was added and the mixture was stirred at 65° for 1 hour. An additional 10 g of zinc was added, and the mixture was stirred 1 hour. The warm mixture was filtered and concentrated *in vacuo*, and the residue was partitioned between ether and 5% hydrochloric acid. The ether was washed with brine, dried over sodium sulfate, and evaporated to give crude **3b** which was purified by silica gel chromatography (50% ether-hexanes) to give 36 g (65%) of **3b**.

4-Cyanoindole (**3d**) and 4-Cyano-1-hydroxyindole (**2d**).

Table II, Entry 8.

A mixture of 3.5 g (16 mmoles) of *trans*-6-cyano-β-dimethylamino-2-nitrostyrene (**1d**) [8] and 75 mg of 10% palladium on carbon in 140 ml of tetrahydrofuran was hydrogenated on a Parr apparatus for 12 hours. The mixture was processed in the usual way and chromatographed on silica gel (1% methanol-dichloromethane) to afford 0.38 g (17%) of **3d** and 1.90 g (75%) of **2d**. Compound **2d** was a white solid which was stable for months at room temperature, mp 126-128°; ir (potassium bromide): 3240, 2230, 1360, 1340 cm^{-1}; nmr (acetone-d_6): δ 6.52 (dd, 1H, J = 3.4, 1 Hz, C_3H), 7.33 (dd, 1H, J = 7.3, 8.3 Hz, C_6H), 7.51 (dd, 1H, J = 7.3, 1 Hz, C_5H), 7.67 (d, 1H, J = 3.4 Hz, C_2H), 7.78 (ddd, 1H, J = 8.3, 1.0, 1.0 Hz, C_7H); ms: m/e 158 (M^+), 141 (M^+-OH), 129, 114, 103.

Anal. Calcd. for $C_9H_6N_2O$ (158.15): C, 68.35; H, 3.82; N, 17.71. Found: C, 68.48; H, 3.50; N, 17.45.

5-Cyano-1-hydroxyindole (**2e**).

Table III, Entry e.

This compound was obtained as previously described for **2d** and rapidly darkened at room temperature. Compound **2e** had mp 83-84°; nmr (acetone-d_6): δ 6.50 (dd, 1H, J = 3.4, 1 Hz, C_3H), 7.45 (dd, 1H, J = 8.5, 1.5 Hz, C_6H), 7.55 (d, 1H, J = 3.4 Hz, C_2H), 7.58 (broad d, 1H, J = 8.5 Hz, C_7H), 8.05 (dd, 1H, J = 1.5, 0.7 Hz, C_4H). Due to instability of this material, a satisfactory combustion analysis was not obtained. Instead, **2e** was converted to 1-acetoxy-5-cyanoindole (**11**) by treatment with acetic anhydride-pyridine. Compound **11** had mp 124-125°.

Anal. Calcd. for $C_{11}H_8N_2O_2$ (200.21): C, 65.99; H, 4.04; N, 14.00. Found: C, 65.91; H, 4.05; N, 13.91.

6-Cyano-1-hydroxyindole (**2f**).

Table III, Entry f.

This compound was obtained as described for **2d** and rapidly decomposed at room temperature. Compound **2f** had mp 109-110°; nmr (acetone-d_6): δ 6.48 (dd, 1H, J = 3.3, 1 Hz, C_3H), 7.30 (dd, 1H, J = 8.0, 1.5 Hz, C_5H), 7.64 (d, 1H, J = 3.3 Hz, C_2H), 7.72 (dd, 1H, J = 8.0, 0.7 Hz, C_4H), 7.84 (m, 1H, C_7H); ms: m/e 158 (M^+), 141 (M^+-OH), 129, 114.

Anal. Calcd. for $C_9H_6N_2O$ (158.15): C, 68.35; H, 3.82; N, 17.71. Found: C, 68.27; H, 3.69; N, 17.57.

7-Cyanoindole (**2g**), 7-Carboxamidoindole (**7**), β-(2-Amino-3-cyanophenyl)ethylamine (**8**) and Di-(7-Indolylmethyl)amine (**9**).

A solution fo 3.5 g (16 mmoles) of **1g** and 0.75 g of 10% palladium on carbon in 140 ml of tetrahydrofuran was hydrogenated at 50 psi for 2 hours. The mixture was filtered and evaporated, and the residue was partitioned between ether and 5% hydrochloric acid. A precipitate of **9** hydrochloride formed and was filtered off (0.18 g, 8%). The ether layer was washed with brine, dried over sodium sulfate and evaporated, and the residue was chromatographed on silica gel (25% ethyl acetate-hexanes) to give 1.0 g (44%) of 7-cyanoindole (**2g**). The 5% hydrochloric acid layer was made basic with ammonium hydroxide and extracted with dichloromethane. The dichloromethane was evaporated and the residue was purified by chromatography on silic gel (5% methanol-dichloromethane) to afford 1.2 g (40%) of **8**. Compound **9** hydrochloride had mp 248-249°; ir 3600-3200, 1460, 1340 cm^{-1}; nmr (DMSO-d_6): δ 4.60 (s, 2H), 6.52 (d, 1H, J = 3 Hz, C_3H), 7.03 (dd, 1H, J = 8.0, 8.0 Hz), 7.25 (d, 1H, J = 8.0 Hz), 7.44 (m, 1H, C_2H), 7.60 (d, 1H, J = 8.0 Hz), 9.50 and 10.80 (exchangeable); ms: m/e 275 (M^+), 146, 145 (indole-CH_2NH), 131, 130 (indole-CH_2).

Anal. Calcd. for $C_{18}H_{17}N_3 \cdot HCl$ (311.8): C, 69.34; H, 5.82; N, 13.47. Found: C, 69.01; H, 5.68; N, 13.09.

Compound **8** had mp 55-56°; ir (potassium bromide): 3500-3200, 2210, 1650, 1630 cm^{-1}; nmr (deuteriochloroform): δ 2.33 (s, 6H), 2.42-2.80 (m, 4H), 5.80 (broad, exchangeable, 2H), 6.60 (dd, 1H, J = 6.0, 6.0 Hz), 7.05-7.33 (m, 2H).

Anal. Calcd. for $C_{11}H_{15}N_3$ (189.26): C, 69.81; H, 7.99; N, 22.20. Found: C, 69.52; H, 7.68; N, 21.81.

When the hydrogenation of **1g** was carried out in benzene or methanol, the amide **7** was isolated by silica gel chromatography (25% ethyl acetate-hexanes) in addition to 7-cyanoindole (**2g**).

Compound **7** had mp 201-202°; ir (potassium bromide): 3440, 3360, 3180, 1660, 1620, 1610, 1590, 1430 cm^{-1}; nmr (DMSO-d_6): 6.48 (m, 1H, sharpens to doublet with deuterium oxide, J = 3.0 Hz, C_3H), 7.05 (dd, 1H, J = 8.0, 8.0 Hz C_5H), 7.35 (m, 1H, sharpens to doublet with deuterium oxide, J = 3.0 Hz, C_2H), 7.40 (s, exchangeable), 7.68 (d, 1H, J = 8.0 Hz), 7.70 (d, 1H, J = 8.0 Hz); ms: m/e 275 (M^+), 146, 145 (d, 1H, J = 8.0 Hz); ms: m/e 160 (M^+), 143, 115.

Anal. Calcd. for $C_9H_8N_2O$ (160.16): C, 67.50; H, 5.03; N, 17.49. Found: C, 67.43; H, 4.77; N, 17.17.

Indole-4-carboxaldehyde (**10**).

Hydrogenation of 67 g (309 mmoles) of **1d** and 2 g of 10% palladium on carbon in 350 ml of tetrahydrofuran for 16 hours followed by standard workup gave a crystalline product which was triturated with petroleum ether and filtered to afford 40 g (≈90%) of a mixture of 2d and **3d** (ratio ≈ 60:40). A mixture of **2d** and **3d** thus obtained (50 g, ≈330 mmoles) was added at once to an ice cold stirred suspension of 100 g (940 mmoles) of sodium hypophosphite hydrate and 130 g of Raney nickel in 500 ml of pyridine, 250 ml of acetic acid, and 250 ml of water. The mixture was stirred for 4 hours at room temperature, filtered through Celite, and the filtrate was concentrated *in vacuo*. The residue was partitioned between ethyl acetate and water, and the ethyl acetate was dried over magnesium sulfate, filtered, and evaporated to afford 43 g (≈90%) of crystalline **10** which was pure by tlc analysis (1% methanol-chloroform). Recrystallization from methanol-water gave an analytical sample, mp 139-140° (lit [18] mp 142-144°).

Acknowledgement.

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[7] The 1-hydroxyindoles **2b** and **2d** are smoothly reduced to indoles **3b** and **3d**, respectively, with zinc in acetic acid at 50-80°. In fact, the Leimgruber-Batcho synthesis of **3b** and **3d** is efficiently carried out from **1b** and **1d** under the same conditions and is an attractive alternate to the iron-acetic acid procedure which has been described in Reference 8.

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[16] We were unable to find a literature melting point for methyl-7-indolecarboxylate. The following physical data were obtained: nmr (deuteriochloroform): δ 3.96 (s, 3H), 6.58 (dd, 1H, J = 1, 2 Hz), 7.13 (dd, 1H, J = 5, 5 Hz), 7.26 (dd, 1H, J = 1, 2 Hz), 7.77-7.98 (m, 2H).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.12; N, 7.99. Found: C, 68.23; H, 5.23; N, 7.89.

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