Synthesis of 1,3-Disubstituted-2-amino-5-hydroxyindoles by Reductive Aromatization

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Reductive aromatization and demethylation of 1,3-disubstituted-2-amino-5-oxo-7a-methyl-5,7a-dihydroindoles with zinc, pyridine and a trace of water yields 1,3-disubstituted-2-amino-5-hydroxyindoles. Simple derivatives of the 5-hydroxy substituent are described.

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Introduction.

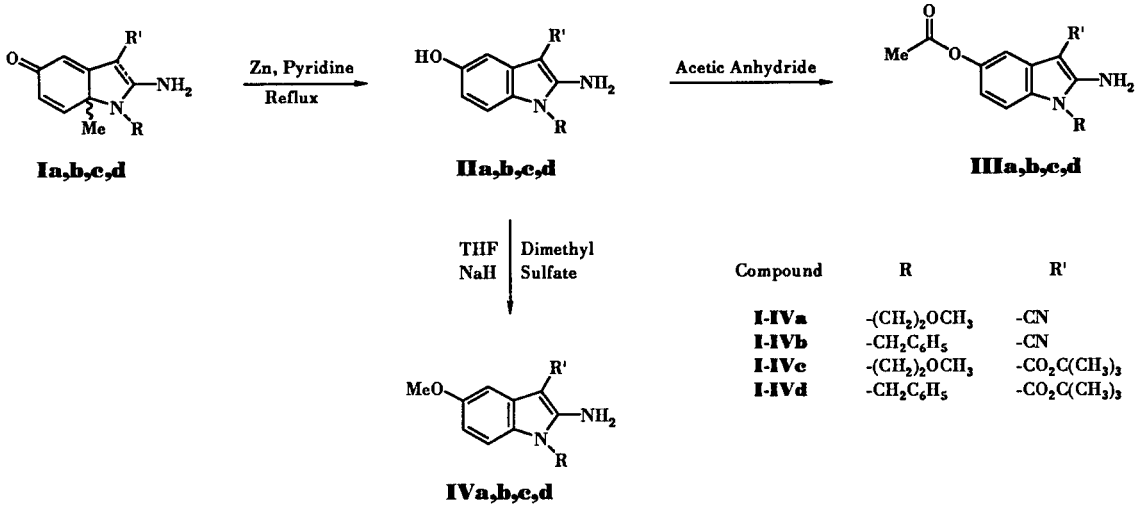
Previous work in our laboratory has involved production of a series of 1,3-disubstituted-2-amino-5-oxo-7a-methyl-5,7a-dihydroindoles by a novel cycloadditon of ethyl propiolate to 1,3-disubstituted-2-amino-4,5-dimethylpyrroles [1]. We have found these pyrroles readily available *via* the condensation of acetoin, a primary amine and α-substituted acetonitriles such as malononitrile or *t*-butyl cyanoacetate [2]. We now wish to report the reductive aromatization of these dihydroindoles with zinc, pyridine and a trace of water, a procedure first used in the production of estrone and other A-ring aromatic corticoids from cross-conjugated dienones and trienones [3,4] (Scheme I).

Methods for the preparation of 2-aminoindoles include Beckmann rearrangements of 2-acylindole oximes [5,6], amination of indole-2-thiones [7] and Curtius degradation of indole-2-carboxylhydrazides [8]. 2-Aminoindole is directly available *via* the cyclization of *o*-aminophenylacetonitrile [9], a reaction which also affords substitution at the 1-position when done in the presence of an alkyl halide [10]. The Nenitzescu synthesis is specific for 5-hydroxyindoles [11] and other procedures [12] afford them as well. Many of these, especially the ring closure methods, are mutually exclusive for the introduction of both functional groups. The parent compound, 2-amino-5-hydroxyindole, has not been reported and substituted variations appear to be rare. The current technology offers a versatile route to these compounds, where the identity of the 1-substituent has little limitation on the scope of the reaction and the 3-substituent is restricted only to an electron-withdrawing group.

2-Aminopyrroles unsubstituted in the 3-position are known to be unstable [13], undergoing air oxidation to iminopyrroles which results in the formation of polymeric products. The air-sensitivity of 2-aminoindoles is also well established [14]. We believe that the electron-withdrawing nature of the 3-substitutent explains the marked stability of these indoles as well as of the 2-amino-4,5-dimethylpyrroles from which they are formed. We have also found the 2-amino substituent of these indoles to be remarkably non-nucleophilic; conditions suitable for *O*-acetylation (100° for 1 hour) resulted in little or no *N*-acetylated product.

2-Aminoindoles have been used in the synthesis of polycylic indoles by a number of groups [15,16]. We are particularly interested in the similarity of these compounds to

Scheme I



Compound	R	R'
I-IVa	$-(CH_2)_2OCH_3$	-CN
I-IVb	$-CH_2C_6H_5$	-CN
I-IVc	$-(CH_2)_2OCH_3$	$-CO_2C(CH_3)_3$
I-IVd	$-CH_2C_6H_5$	$-CO_2C(CH_3)_3$

known 5-HT_3 ligands. 2-Methyl-5-hydroxytryptamine displays high potency for this receptor [17] and indole-3-carboxylate is the aryl nucleus of another potent 5-HT_3 antagonist with antiemetic efficacy, ICS 205-930 [18]. Conceivably, functional group manipulation at the 3-position of the compounds in the present work may yield agents which conform to recently proposed pharmacophore models [19-21].

EXPERIMENTAL

The melting points were determined on an Electrothermal apparatus and are uncorrected. The infrared spectra were determined on a Beckman Acculab 4 spectrophotometer using the potassium bromide technique. The tlc were performed with Merck silica gel plates, type 60-F_{254}. The mplc were performed with 32-63 μm silica gel from Selecto, Inc., Kennesaw, GA. Mass spectroscopy was performed using a heated direct insertion probe on a VG-70 SQ at 70 eV. The proton nmr spectra were obtained on a Bruker AM 500 FT-NMR spectrometer in acetone-d_6 using default parameters (number of scans 32, acquisition time 3.277 s, delay 1s and a tip angle of 30 degrees). Zinc dust was activated [22] by sequential washing in 10% aqueous hydrochloric acid, water and acetone.

Representative Procedure for the Preparation of the 1,3-Disubstituted-2-amino-5-oxo-7a-methyl-5,7a-dihydroindoles **Ia-d** from 1,3-Substituted-2-amino-4,5-dimethylpyrroles and Ethyl Propiolate.

1-(2-Methoxyethyl)-2-amino-3-cyano-5-oxo-7a-methyl-5,7a-dihydroindole (**Ia**).

Ethyl propiolate (0.044 mole, 4.32 g) was added to a stirred solution of 1-(2-methoxyethyl)-2-amino-3-cyano-4,5-dimethylpyrrole (0.044 mole, 8.50 g) in 100 ml of absolute ethanol. The reaction mixture was stirred at room temperature for one hour, refluxed for two hours, then concentrated *in vacuo* to a thick brown oil. The oil was triturated with 200 ml of a hexanes:ethyl acetate solution (1:1), cooled to 0° and the precipitate was collected by filtration. Recrystallization (ethyl acetate) yielded (2.73 g, 25%) orange crystals, tlc Rf, hexanes:ethyl acetate (1:1), 0.02, mp 231-232° dec; ir: ν 3300, 3100, 2190, 1620, 1440, 1350, 1250, 1200, 1080 cm^{-1}; ^{1}H-nmr: δ 1.62 (s, 3H, 7a-CH_3), 3.39 (s, 3H, $NCH_2CH_2OCH_3$), 3.64 (t, 2H, $NCH_2CH_2OCH_3$), 3.76 (t, 2H, $NCH_2CH_2OCH_3$), 5.40 (d, 1H, 4-*H*, J = 1.7 Hz), 5.87 (dd, 1H, 6-*H*, J = 1.7, 9.8 Hz), 7.14 (d, 1H, 7-*H*, J = 9.9 Hz), 7.22 (br s, 2H, NH_2); hrms: (m/z) 245.1155, error 3.7 ppm, (M^+) and base peak.

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.47; H, 6.22; N, 16.99.

General Procedure for the Preparation of the 1,3-Disubstituted-2-amino-5-hydroxyindoles **IIa-d**.

The appropriate 1,3-disubstituted-2-amino-5-oxo-7a-methyl-5,7a-dihydroindole **Ia-d** (0.003 mole) was dissolved in 60 ml of pyridine and 0.4 ml of water. To this solution was added 40 g of freshly activated zinc dust. The reaction mixture was stirred at reflux for 2 hours and then cooled. The zinc dust was removed by filtration and the pyridine removed *in vacuo*. The product was eluted by mplc with a hexanes:ethyl acetate (1:1) mobile phase.

1-(2-Methoxyethyl)-2-amino-3-cyano-5-hydroxyindole (**IIa**).

This compound was obtained as pale yellow crystals (0.30 g, 44%); tlc Rf, hexanes:ethyl acetate (1:1), 0.30, mp 200-200.5°; ir: ν 3320, 2980, 1610, 1490, 1460, 1370, 1120 cm^{-1}; ^{1}H-nmr: δ 3.33 (s, 3H, $NCH_2CH_2OCH_3$), 3.70 (t, 2H, $NCH_2CH_2OCH_3$), 4.22 (t, 2H, $NCH_2CH_2OCH_3$), 5.98 (br s, 2H, NH_2), 6.56 (m, 1H, 6-*H*), 6.75 (m, 1H, 4-*H*), 7.08 (m, 1H, 7-*H*); hrms: (m/z) 231.1009, error 0.4 ppm, (M^+) and base peak.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.33; H, 5.67; N, 18.17. Found: C, 62.17; H, 5.74; N, 18.15.

1-Benzyl-2-amino-3-cyano-5-hydroxyindole (**IIb**).

This compound was obtained as off-white crystals (0.69 g, 88%), tlc Rf, hexanes:ethyl acetate (1:1), 0.38, mp 224-224.5°; ir: ν 3420, 3340, 2195, 1640, 1620, 1540, 1470, 1340, 1210, 1160 cm^{-1}; ^{1}H-nmr: δ 5.34 (s, 2H, N-CH_2-benzyl), 6.26 (br s, 2H, NH_2), 6.50 (m, 1H, 6-*H*), 6.78 (m, 1H, 4-*H*), 6.98 (m, 1H, 7-*H*), 7.15 (m, 2H, *o*-benzyl *H*), 7.30 (m, 3H, *m* and *p*-benzyl *H*); hrms: (m/z) 263.1059, error 0.4 ppm, (M^+), 91, base peak (benzyl$^+$).

Anal. Calcd. for $C_{16}H_{13}N_3O$: C, 72.99; H, 4.98; N, 15.96. Found: C, 72.89; H, 5.02; N, 15.91.

1-(2-Methoxyethyl)-2-amino-3-*tert*-butoxycarbonyl-5-hydroxyindole (**IIc**).

This compound was obtained as a white foam (0.51 g, 56%), tlc Rf, hexanes:ethyl acetate (1:1), 0.31; ir: ν 3320, 2980, 1610, 1500, 1460, 1360, 1100 cm^{-1}; ^{1}H-nmr: δ 1.60 (s, 9H, *t*-butyl CH_3), 3.32 (s, 3H, $NCH_2CH_2OCH_3$), 3.69 (t, 2H, $NCH_2CH_2OCH_3$), 4.17 (t, 2H, $NCH_2CH_2OCH_3$), 6.38 (br s, 2H, NH_2), 6.50 (m, 1H, 6-*H*), 7.01 (m, 1H, 7-*H*), 7.26 (m, 1H, 4-*H*); hrms: (m/z) 306.1585, error 1.6 ppm (M^+), 250, base peak, (M^+-C_4H_8).

Anal. Calcd. for $C_{16}H_{22}N_2O_4$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.62; H, 7.29; N, 9.04.

1-Benzyl-2-amino-3-*tert*-butoxycarbonyl-5-hydroxyindole (**IId**).

This compound was obtained as an off-white foam (0.85 g, 84%), tlc Rf, hexanes:ethyl acetate, (1:1), 0.68; ir: ν 3340, 1580, 1450, 1355, 1240, 1100 cm^{-1}; ^{1}H-nmr: δ 1.62 (s, 9H, *t*-butyl CH_3), 5.29 (s, 2H, N-CH_2-benzyl), 6.44 (m, 1H, 6-*H*), 6.63 (br s, 2H, NH_2), 6.90 (m, 1H, 7-*H*), 7.16 (m, 1H, 4-*H*), 7.21 (m, 5H, benzyl *H*); hrms: (m/z) 338.1627, error 0.9 ppm, (M^+), 282, base peak (M^+-C_4H_8).

Anal. Calcd. for $C_{20}H_{22}N_2O_3 \cdot 0.25\ H_2O$: C, 70.05; H, 6.61; N, 8.17. Found: C, 69.95; H, 6.77; N, 8.02.

General Procedure for the Preparation of 1,3-Disubstituted-2-amino-5-acetoxyindoles (**IIIa-d**).

Acetic anhydride (15 ml) was stirred with **IIa-d** (0.002 mole) for 1 hour on a steam bath. The reaction mixture was cooled and 200 ml of ethyl acetate was added. This solution was washed succesively with distilled water, 1*N* sodium hydroxide, saturated sodium chloride, then dried with anhydrous magnesium sulfate. The ethyl acetate was concentrated *in vacuo* and the product eluted *via* mplc with a hexane:ethyl acetate (1:1) mobile phase.

1-(2-Methoxyethyl)-2-amino-3-cyano-5-acetoxyindole (**IIIa**).

This compound was obtained as pale pink crystals (0.44 g, 80%), tlc Rf, hexanes:ethyl acetate (1:1), 0.30, mp 166-168°; ir: ν 3400, 3310, 2190, 1740, 1620, 1540, 1460, 1355, 1200, 1120 cm^{-1}; ^{1}H-nmr: δ 2.25 (s, 3H, acetoxy CH_3), 3.33 (s, 3H, $NCH_2CH_2OCH_3$), 3.74 (t, 2H, $NCH_2CH_2OCH_3$), 4.30 (t, 2H, $NCH_2CH_2OCH_3$), 6.21 (br s, 2H, NH_2), 6.75 (m, 1H, 6-*H*), 7.00 (m, 1H, 4-*H*), 7.26 (m, 1H,

7-*H*); hrms: (m/z) 273.1113, error 3.3 ppm (M^+), 231, base, (M^+-C_2H_2O).

Anal. Calcd. for $C_{14}H_{15}N_3O_3$: C, 61.53; H, 5.53; N, 15.38. Found: C, 61.48; H, 5.54; N, 15.28.

1-Benzyl-2-amino-3-cyano-5-acetoxyindole (**IIIb**).

This compound was obtained as off-white crystals (0.53 g, 86%), tlc Rf, hexanes:ethyl acetate (1:1), 0.46, mp 212-213°; ir: ν 3395, 3340, 3240, 2195, 1730, 1650, 1560, 1470, 1205, 1140 cm^{-1}; ^{1}H-nmr: δ 2.24 (s, 3H, acetoxy C*H*$_3$), 5.43 (s, 2H, N-C*H*$_2$-benzyl), 6.50 (br s, 2H, N*H*$_2$), 6.70 (m, 1H, 6-*H*), 7.03 (m, 1H, 4-*H*), 7.16 (m, 1H, 7-*H*), 7.17 (m, 2H, *o*-benzyl *H*), 7.28 (m, 3H, *m* and *p*-benzyl *H*); hrms: (m/z) 305.1160, error 1.3 ppm, (M^+), 263 base peak (M^+-C_2H_2O).

Anal. Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.73; H, 4.99; N, 13.66.

1-(2-Methoxyethyl)-2-amino-3-*tert*-butoxycarbonyl-5-acetoxyindole (**IIIc**).

This compound was obtained as off-white crystals (0.55 g, 79%), tlc Rf, hexanes:ethyl acetate (1:1), 0.38, mp 119-121°; ir: ν 3405, 3320, 2960, 1750, 1600, 1460, 1360, 1270, 1200, 1100 cm^{-1}; ^{1}H-nmr: δ 1.60 (s, 9H, *t*-butyl C*H*$_3$), 2.24 (s, 3H, acetoxy C*H*$_3$), 3.32 (s, 3H, NCH$_2$CH$_2$OC*H*$_3$), 3.72 (t, 2H, NC*H*$_2$CH$_2$OCH$_3$), 4.25 (t, 2H, NCH$_2$C*H*$_2$OCH$_3$), 6.49 (br s, 2H, N*H*$_2$), 6.70 (m, 1H, 6-*H*), 7.18 (m, 1H, 7-*H*), 7.41 (m, 1H, 4-*H*); hrms: (m/z) 348.1668, error 4.9 ppm (M^+), 250, base peak, (M^+-C_4H_8).

Anal. Calcd. for $C_{18}H_{24}N_2O_5$: C, 62.05; H, 6.94; N, 8.04. Found: C, 62.20; H, 6.96; N, 8.07.

1-Benzyl-2-amino-3-*tert*-butoxycarbonyl-5-acetoxyindole (**IIId**).

This compound was obtained as off-white crystals (0.35 g, 46%), tlc Rf, hexanes:ethyl acetate (1:1), 0.75, mp 209-210°; ir: ν 3440, 3350, 2960, 1735, 1600, 1440, 1350, 1205, 1100 cm^{-1}; ^{1}H-nmr: δ 1.62 (s, 9H, *t*-butyl C*H*$_3$), 2.22 (s, 3H, acetoxy C*H*$_3$), 5.38 (s, 2H, N-C*H*$_2$-benzyl), 6.48 (m, 1H, 6-*H*), 6.70 (br s, 2H, N*H*$_2$), 7.08 (m, 1H, 7-*H*), 7.17 (m, 2H, *o*-benzyl *H*), 7.26 (m, 3H, *m* and *p*-benzyl *H*), 7.43 (m, 1H, 4-*H*); hrms: (m/z) 380.1737, error 0.3 ppm, (M^+), 324, base peak (M^+-C_4H_8).

Anal. Calcd. for $C_{22}H_{24}N_2O_4$: C, 69.46; H, 6.36; N, 7.36. Found: C, 69.47; H, 6.39; N, 7.36.

General Procedure for the Preparation of 1,3-Disubstituted-2-amino-5-methoxyindoles **IVa-d**.

Sodium hydride (0.07 g, 0.003 mole) and **IIa-d** (0.002 mole) were dissolved in 100 ml of dry THF. Dimethyl sulfate (0.002 mole) was added to the flask which was then heated at reflux for two hours. The reaction mixture was cooled, the excess sodium hydride was destroyed with methanol and the solvent was removed *in vacuo*. The product was eluted *via* mplc with a hexane:ethyl acetate (1:1) mobile phase.

1-(2-Methoxyethyl)-2-amino-3-cyano-5-methoxyindole (**IVa**).

This compound was obtained as off-white crystals (0.45 g, 92%), tlc Rf, hexanes:ethyl acetate (1:1), 0.43, mp 156-157°; ir: ν 3420, 3340, 2880, 2190, 1615, 1540, 1480, 1230, 1160, 1105 cm^{-1}; ^{1}H-nmr: δ 3.32 (s, 3H, NCH$_2$CH$_2$OC*H*$_3$), 3.71 (t, 2H, NC*H*$_2$CH$_2$OCH$_3$), 3.81 (s, 3H, OC*H*$_3$), 4.25 (t, 2H, NCH$_2$C*H*$_2$OCH$_3$), 6.04 (br s, 2H, N*H*$_2$), 6.63 (m, 1H, 6-*H*), 6.83 (m, 1H, 4-*H*), 7.17 (m, 1H, 7-*H*); hrms: (m/z) 245.1164, error 0 ppm (M^+) and base peak.

Anal. Calcd. for $C_{13}H_{15}N_3O_2$: C, 63.66; H, 6.16; N, 17.13. Found: C, 63.74; H, 6.22; N, 17.21.

1-Benzyl-2-amino-3-cyano-5-methoxyindole (**IVb**).

This compound was obtained as a stiff, tan foam (0.19 , 34%), tlc Rf, hexanes:ethyl acetate (1:1), 0.57; ir: ν 3370, 3240, 2195, 1620, 1540, 1470, 1160 cm^{-1}; ^{1}H-nmr: δ 3.80 (s, 3H, OC*H*$_3$), 5.37 (s, 2H, N-C*H*$_2$-benzyl), 6.32 (br s, 2H, N*H*$_2$), 6.57 (m, 1H, 6-*H*), 6.86 (m, 1H, 4-*H*), 7.05 (m, 2H, *o*-benzyl *H*), 7.15 (m, 1H, 7-H), 7.30 (m, 3H, *m* and *p*-benzyl *H*); hrms: (m/z) 277.1217, error 0.7 ppm, (M^+), 91, base peak (benzyl$^+$).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.77; H, 5.70; N, 15.15.

1-(2-Methoxyethyl)-2-amino-3-*tert*-butoxycarbonyl-5-methoxyindole (**IVc**).

This compound was obtained as white crystals (0.61 g, 96%), tlc Rf, hexanes:ethyl acetate (1:1), 0.47, mp 95.5-97°; ir: ν 3410, 3320, 2940, 1580, 1450, 1350, 1100 cm^{-1}; ^{1}H-nmr: δ 1.63 (s, 9H, *t*-butyl C*H*$_3$), 3.31 (s, 3H, NCH$_2$CH$_2$OC*H*$_3$), 3.69 (t, 2H, NC*H*$_2$CH$_2$OCH$_3$), 3.79 (s, 3H, OC*H*$_3$), 4.20 (t, 2H, NCH$_2$C*H*$_2$OCH$_3$), 6.41 (br s, 2H, N*H*$_2$), 6.58 (m, 1H, 6-*H*), 7.09 (m, 1H, 7-*H*), 7.33 (m, 1H, 4-*H*); hrms: (m/z) 320.1719, error 5 ppm (M^+), 264, base peak, (M^+-C_4H_8).

Anal. Calcd. for $C_{17}H_{24}N_2O_4$: C, 63.73; H, 7.55; N, 8.74. Found: C, 63.79; H, 7.63; N, 8.70.

1-Benzyl-2-amino-3-*tert*-butoxycarbonyl-5-methoxyindole (**IVd**).

This compound was obtained as off-white crystals (0.22 g, 32%), tlc Rf, hexanes:ethyl acetate (1:1), 0.82, mp 129-130°; ir: ν 3480, 3360, 2980, 1595, 1460, 1360, 1230, 1200, 1140, 1105 cm^{-1}; ^{1}H-nmr: δ 1.63 (s, 9H, *t*-butyl C*H*$_3$), 3.77 (s, 3H, OC*H*$_3$), 5.33 (s, 2H, N-C*H*$_2$-benzyl), 6.52 (m, 1H, 6-*H*), 6.66 (br s, 2H, N*H*$_2$), 7.00 (m, 1H, 7-*H*), 7.15 (m, 1H, 4-*H*), 7.25 (m, 2H, *o*-benzyl *H*), 7.30 (m, 3H, *m* and *p*-benzyl *H*); hrms: (m/z) 352.1784, error 0.9 ppm, (M^+), 296, base peak (M^+-C_4H_8).

Anal. Calcd. for $C_{21}H_{24}N_2O_3$: C, 71.57; H, 6.86; N, 7.95. Found: C, 71.67; H, 6.89; N, 7.91.

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