Simple Synthesis of Some 2-Substituted Melatonin Derivatives

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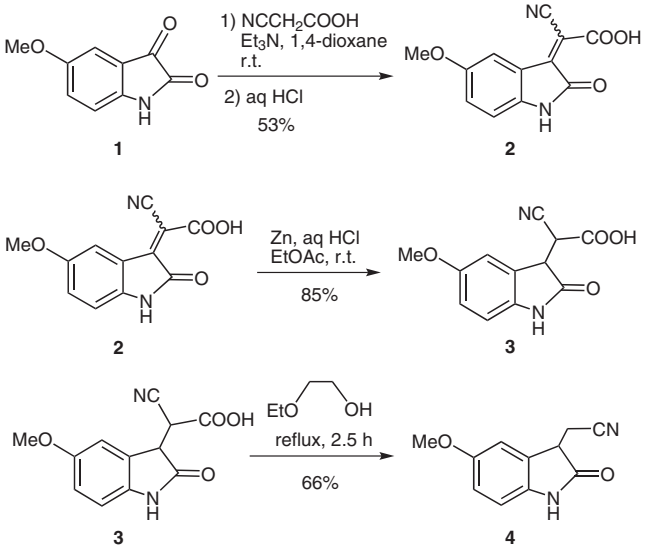
Abstract: A simple strategy for the synthesis of some 2-substituted melatonin derivatives using *p*-anisidine as starting material is reported. The key step is a chemoselective reduction of a cyano group in the presence of an appropriate acid anhydride by hydrogenation over Adams' catalyst or with sodium borohydride in the presence of catalytic amounts of anhydrous nickel(II) chloride. The 2-substituted melatonin derivatives were obtained in six or seven steps from inexpensive *p*-anisidine in 9–13% overall yield.

Key words: indoles, melatonin derivatives, reductions, medicinal chemistry

Melatonin (*N*-acetyl-5-methoxytryptamine) is the principle neurohormone secreted by the pineal gland.[1] Its medicinal use is restricted due to low selectivity and too broad spectrum of action. The search for melatonin analogues with greater selectivity is very important. Two subtypes (Mel1a and Mel1b) of human melatonin receptors are known. A recent molecular modeling study[2a] and additional experimental data[2b] have shown that melatonin derivatives with bulky substituents at position 2 exhibited a greater affinity for Mel1b melatonin receptors than for Mel1a receptors. In the case of halogens, 2-bromomelatonin[3] is more selective and exhibits a greater affinity for Mel1b receptors than 2-iodomelatonin, a useful ligand for both melatonin receptor subtypes. 2-Chloromelatonin, proposed to have a much greater selectivity, has been previously mentioned as a low-yield product of direct chlorination of melatonin.[4] In this study, we report a simple strategy for the synthesis of 2-chloromelatonin and 2-oxo-2,3-dihydromelatonin, and derivatives, in good overall yield.

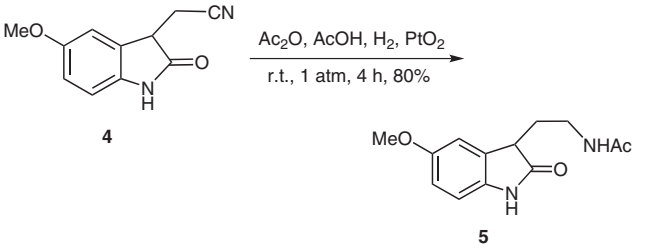
Cyano compound **2** was prepared as a mixture of stereoisomers via Knoevenagel condensation of 5-methoxyisatin (5-methoxyindoline-2,3-dione, **1**) with cyanoacetic acid using the method of Pietra[5] (Scheme 1). It has been previously reported that hydrogenation of compound **2** in the presence of palladium on carbon led to a selective reduction of the carbon–carbon double bond.[6] We have found that the use of the less expensive reduction system zinc dust–aqueous hydrochloric acid resulted in a high yield of compound **3**. The key compound for further synthesis, (5-methoxy-2-oxoindolin-3-yl)acetonitrile (**4**),



Scheme 1

was prepared via decarboxylation of acid **3** in 2-ethoxyethanol (Scheme 1).

Cyano compound **4** was hydrogenated using Adams' catalyst (PtO_2) in a mixture of acetic acid and acetic anhydride at room temperature and atmospheric pressure. 2-Oxo-2,3-dihydromelatonin (**5**) was obtained in high yield (Scheme 2).



Scheme 2

(2-Chloro-5-methoxy-1*H*-indol-3-yl)acetonitrile (**6**) was prepared by refluxing (5-methoxy-2-oxoindolin-3-yl)acetonitrile (**4**) in phosphorus oxychloride (Scheme 3).

Further hydrogenation of compound **6** in the presence of Adams' catalyst led to dechlorination of the indole, and no 2-chloromelatonin was obtained. Selective nitrile reduction was achieved using sodium borohydride in methanol in the presence of catalytic amounts of anhydrous nickel(II) chloride. Addition of acetic anhydride to the reduc-

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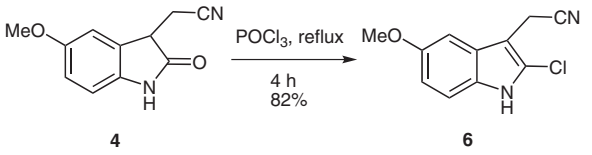
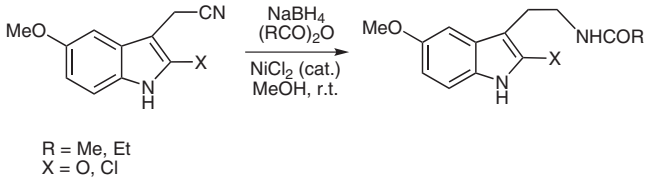


4 6

Scheme 3



R = Me, Et
X = O, Cl

Scheme 4

Table 1 Yields and Conditions for the Reduction of Nitriles **4** and **6**

Entry	R	X	Method[a]	Yield (%)
1	Me	OH	A	80
2	Me	OH	B	37
3	Et	OH	B	68
4	Me	Cl	A	–
5	Me	Cl	B	55
6	Et	Cl	B	12

[a] Method A: H_2, Ac_2O, AcOH, PtO_2, r.t., 4 h; Method B: $NaBH_4$, $(RCO)_2O$, $NiCl_2$ (cat.), MeOH, r.t., 4 d.

tion mixture allowed 2-chloromelatonin to be obtained, in good yield (Scheme 4; Table 1, entry 5).

2-Oxo-2,3-dihydromelatonin (**5**) was also obtained by the reduction of nitrile **4** with sodium borohydride in methanol in the presence of acetic anhydride and nickel(II) chloride, in lower yield than the Adams' catalyst supported hydrogenation (Table 1, cf. entries 1 and 2).

Propionic anhydride, instead of acetic anhydride, can also be used for the synthesis of melatonin analogues (Table 1, entries 3 and 6).

In conclusion, a simple strategy for the synthesis of 2-chloromelatonin, 2-oxo-2,3-dihydromelatonin, and derivatives was devised. The binding affinity of all synthesized compounds to melatonin receptors is under investigation.

Melting points were determined on an Electrothermal 9100 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded at 400.13 MHz on a Bruker Avance 400 spectrometer. The ^{1}H chemical shifts (δ) are reported in ppm using TMS as standard internal reference (δ = 0). Coupling constants (*J*) are given in Hz. IR spectra were recorded in vaseline oil with a Specord UR-20 spectrometer. The reaction processes and the purity of the products were monitored by thin-layer chromatography (TLC) on Silufol UV-254 plates with EtOAc as eluent. Liquid chromatography was carried out with Merck silica gel (40/60). Mass spectra (MS) were recorded with a Finnigan MAT INCOSSO spectrometer (electron impact, 70 eV).

2-(Hydroxyimino)-*N*-(4-methoxyphenyl)acetamide

In a 4-L glass flask, a soln of chloral hydrate (145.6 g, 0.88 mol) and Na_2SO_4 (500.0 g, 3.5 mol) in H_2O (2 L) was heated at 65 °C with stirring, then a warm soln of *p*-anisidine (98.4 g, 0.8 mol) in 36% aq HCl (68 mL) and H_2O (480 mL) was added. After the temperature reached 75 °C, a soln of hydroxylamine hydrochloride (88.8 g, 1.27 mol) in H_2O (400 mL) was added. The heating source was turned off, and the solution was cooled to r.t. with stirring. The light-brown precipitate was collected by filtration; yield: 97.5 g (63%); mp 184–185 °C (Lit.[7] 184–185 °C). The product was used without further purification.

5-Methoxyisatin (1)

A mixture of H_2O (17 mL) and concd H_2SO_4 (88 mL) was heated to 75 °C with stirring in a 250-mL three-neck flask. 2-(Hydroxyimino)-*N*-(4-methoxyphenyl)acetamide (25 g, 0.13 mol) was added in portions of ca. 1–2 g for 1.5–2 h and the temperature was kept in the range 65–80 °C during the reaction. After the addition, the still warm (ca. 50–60 °C) mixture was poured into ice water. The dark brown precipitate was collected, washed with H_2O, dried and recrystallized (AcOH) to give a brown-red solid; yield: 20.25 g (88%); mp 201–205 °C (AcOH) (Lit.[6a] 204–204.5 °C).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 3.74 (s, 3 H, OCH_3), 6.83–6.85 (d, *J* = 8.6 Hz, 1 H), 7.06 (s, 1 H), 7.16–7.18 (dd, *J* = 2.5, 7.6 Hz, 1 H), 10.86 (s, 1 H, NH).

Cyano(5-methoxy-2-oxoindolin-3-ylidene)acetic Acid (2)

A mixture of 5-methoxyisatin (**1**; 10.3 g, 0.06 mol), 1,4-dioxane (30 mL), cyanoacetic acid (4.94 g, 0.06 mol) and Et_3N (9.68 mL, 0.072 mol) was placed into a 100-mL flat-bottom flask. The mixture was vigorously stirred (4 h) at 25 °C. After the reaction had ended (monitored by TLC), concd HCl (30 mL) was added. The mixture was kept at 25 °C for 3 d; the obtained precipitate was collected by filtration and dried, giving a dark product as a mixture of stereoisomers (3:2, according to ^{1}H NMR spectroscopy); yield: 7.8 g (53%); mp 193–210 °C (Lit.[5] 194–195 °C).

IR (vaseline oil): 2315–2340 (NH), 2230 (CN), 1730 (COOH), 1640 cm^{-1} (CONHR).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 3.69 (s, 3 H, major product), 3.74 (s, 3 H, minor product), 6.76–6.80 (d, *J* = 8.6 Hz, 2 H), 7.00–7.09 (m, 1 H), 7.36–7.43 (m, 2 H), 7.69 (d, *J* = 2.5 Hz, 1 H), 10.83 (s, 1 H).

Anal. Calcd for $C_{12}H_8N_2O_4$: C, 59.02; H, 3.30; N, 11.47. Found: C, 59.23; H, 3.47; N, 11.35.

Cyano(5-methoxy-2-oxoindolin-3-yl)acetic Acid (3)

To a soln of cyano(5-methoxy-2-oxoindolin-3-ylidene)acetic acid (**2**; 2.537 g, 0.01 mol) in EtOAc (42.4 mL) was added 3 N aq HCl (10.2 mL, 0.03 mol) and zinc powder (1.2 g, 0.02 mol). The reaction was carried out with vigorous stirring at r.t. Completion of the reaction was indicated by a color change from purple to bright yellow. It is worth noting that sometimes the color change could be a reversible process (i.e., the yellow solution became purple again after several minutes); in that case, more zinc and aq HCl should be added. Afterwards, the organic layer was separated, dried (Na_2SO_4) and concentrated. The title compound was isolated as a mixture of two diastereomers (3:2, according to ^{1}H NMR spectroscopy); yield: 2.09 g (85%); tan solid; mp 185 °C (Lit.[6b] 184–185 °C).

IR (vaseline oil): 2315–2340 (NH), 1950 (br, CN), 1730 (COOH), 1650 cm^{-1} (br, CONHR).

^{1}H NMR (400.13 MHz, DMSO-d_6): δ = 3.69 (s, 3 H, OCH_3, minor isomer), 3.71 (s, 3 H, OCH_3, major isomer), 4.08 (d, *J* = 3.2 Hz, 1 H, CH, minor isomer), 4.16 (d, *J* = 4.0 Hz, 1 H, CH, major isomer), 4.82 (d, *J* = 3.2 Hz, 1 H, CH, minor isomer), 4.95 (d, *J* = 4.0 Hz, 1

H, CH, major isomer), 6.80 (m, 5 H, ArH), 7.07 (s, 1 H, ArH), 10.42 (s, 1 H, NH, major isomer), 10.51 (s, 1 H, NH, minor isomer).

(5-Methoxy-2-oxoindolin-3-yl)acetonitrile (4)

A soln of cyano(5-methoxy-2-oxoindolin-3-yl)acetic acid (**3**; 2 g, 0.008 mol) in 2-ethoxyethanol (10 mL) was heated under reflux for 2.5 h with stirring. Afterwards, the mixture was concentrated under reduced pressure and the dark oil was dissolved in warm EtOAc. The solution was passed through a silica gel column, which gave a light-orange solid after evaporation of the EtOAc; yield: 1.09 g (66%); mp 155–160 °C (Lit.[6b] 180–181 °C).

IR (vaseline oil): 2315–2340 (NH), 2280 (CN), 1700 (br, CONHR), 1620 cm^{-1} (C=C).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 2.77 (dd, *J* = 17.0, 9.1 Hz, 1 H, CH_2), 3.10 (dd, *J* = 17.0, 4.8 Hz, 1 H, CH_2), 3.70 (dd, *J* = 8.6, 4.8 Hz, 1 H, CH), 3.81 (s, 3 H, OCH_3), 6.89 (dd, *J* = 8.6, 8.6 Hz, 1 H, ArH), 7.02 (s, 1 H, ArH), 7.20 (d, *J* = 8.6 Hz, 1 H, ArH), 8.45 (s, 1 H, NH).

MS (EI, 70 eV): *m*/*z* (%) = 202 (25), 175 (2), 162 (100), 147 (14), 131 (13), 119 (18), 104 (11), 91 (9), 77 (14).

***N*-[2-(5-Methoxy-2-oxoindolin-3-yl)ethyl]acetamide (2-Oxo-2,3-dihydromelatonin, 5)**

Method A (Scheme 2)

(5-Methoxy-2-oxoindolin-3-yl)acetonitrile (**4**; 1 g, 0.005 mol) was hydrogenated over Adams' catalyst (50 mg, 0.22 mmol) in the presence of Ac_2O (0.5 mL) in glacial AcOH (15 mL) at atmospheric pressure and r.t. Hydrogenation was continued until 0.222 L of H_2 was absorbed (nearly 4 h). The catalyst was filtered off and the solution was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 mL), which was then washed with dilute aq $NaHCO_3$ (10 mL) and concentrated; yield: 1 g (80%); mp 138–146 °C (dec).

Method B (Table 1, Entry 2)

(5-Methoxy-2-oxoindolin-3-yl)acetonitrile (**4**; 0.436 g, 2.2 mmol), MeOH (10 mL), Ac_2O (0.63 mL, 6.7 mmol) and anhyd $NiCl_2$ (0.018 g, 0.14 mmol) were placed into a 30-mL flask. $NaBH_4$ (0.18 g, 4.7 mmol) was added at 0 °C. The mixture was stirred at 25 °C for 4 d, and $NaBH_4$ (0.04 g) was added once per day. When the reaction was complete, the MeOH was evaporated under reduced pressure and the residue was washed with aq K_2CO_3. The product was extracted with EtOAc (2 × 10 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure; yield: 0.2 g (37%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.95 (s, 3 H, CH_3), 1.98–2.09 (m, 1 H), 2.17–2.24 (m, 1 H), 3.41–3.51 (m, 3 H), 3.77 (s, 3 H, OCH_3), 6.58 (br s, 1 H, NH), 6.72–6.75 (dd, *J* = 10.6, 6.4 Hz, 1 H), 6.79–6.81 (d, *J* = 8.4 Hz, 1 H), 6.90 (s, 1 H), 9.04 (s, 1 H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 23.04, 29.94, 36.96, 44.75, 55.76, 110.38, 111.09, 112.75, 130.59, 135.01, 155.76, 170.82, 180.47.

MS (EI, 70 eV): *m*/*z* (%) = 248 (35), 205 (7) [$M^+ - CH_3CO$], 189 (45), 176 (100) [$M^+ - CH_3CONHCH_2$], 163 (17), 117 (23), 83 (38).

Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.70; H, 6.31; N, 11.12.

***N*-[2-(5-Methoxy-2-oxoindolin-3-yl)ethyl]propanamide (Table 1, Entry 3)**

(5-Methoxy-2-oxoindolin-3-yl)acetonitrile (**4**; 0.211 g, 0.001 mol), MeOH (10 mL), propionic anhydride (0.3 mL, 0.0023 mol) and anhyd $NiCl_2$ (0.027 g, 0.21 mmol) were placed into a 30-mL flask. $NaBH_4$ (0.2 g, 5.3 mmol) was added at 0 °C. The mixture was stirred at 25 °C for 4 d, and $NaBH_4$ (0.1 g) was added twice per day. When the reaction was complete, the MeOH was evaporated under reduced pressure and the residue was washed with aq K_2CO_3. The product was extracted with EtOAc (2 × 10 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure; yield: 0.177 g (68%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.26 (t, 3 H), 2.04–2.08 (m, 3 H), 2.18–2.28 (m, 2 H), 3.20–3.27 (m, 1 H), 3.73 (s, 3 H), 6.68 (m, 2 H), 6.93 (s, 1 H).

(2-Chloro-5-methoxy-1*H*-indol-3-yl)acetonitrile (6)

A mixture of (5-methoxy-2-oxoindolin-3-yl)acetonitrile (**4**; 0.1 g, 0.5 mmol) and pure $POCl_3$ (5 mL) was heated under reflux for 4 h with stirring. After the reaction was complete, the excess $POCl_3$ was evaporated under reduced pressure. The residue was washed with aq K_2CO_3 and extracted with CH_2Cl_2 (2 × 10 mL). The organic layer was dried (Na_2SO_4) and concentrated to give a beige solid; yield: 0.09 g (82%); mp 135–136 °C.

IR (film): 2650–2800 (NH), 2270 (CN), 1700, 1600 cm^{-1} (C=C).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 3.77 (s, 2 H), 3.88 (s, 3 H), 6.89 (dd, *J* = 8.8, 2.3 Hz, 1 H), 7.02 (s, 1 H), 7.19 (d, *J* = 8.9 Hz, 1 H), 8.45 (s, 1 H, NH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.96, 22.69, 29.70, 55.85, 99.72, 111.83, 113.22, 115.00, 126.64, 129.19, 154.95.

MS (EI, 70 eV): *m*/*z* (%) = 220 (100) [M^+], 205 (75), 194 (7), 185 (35), 177 (85), 170 (7), 162 (10), 148 (35), 142 (32), 134 (7), 120 (15).

***N*-[2-(2-Chloro-5-methoxy-1*H*-indol-3-yl)ethyl]acetamide (2-Chloromelatonin; Table 1, Entry 5)**

(2-Chloro-5-methoxy-1*H*-indol-3-yl)acetonitrile (**6**; 0.150 g, 0.68 mmol), MeOH (3.58 mL), Ac_2O (0.13 mL, 1.4 mmol) and anhyd $NiCl_2$ (0.018 g, 0.138 mmol) were placed into a 30-mL flask. $NaBH_4$ (0.18 g, 4.7 mmol) was added at 0 °C. The mixture was stirred at 25 °C for 4 d, and $NaBH_4$ (0.15 g) was added once per day. When the reaction was complete, the MeOH was evaporated under reduced pressure and the residue was washed with aq K_2CO_3. The product was extracted with EtOAc (2 × 5 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure; yield: 0.1 g (55%); mp 120–130 °C (dec) (Lit.[4] 124 °C).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.93 (s, 3 H, CH_3), 2.92 (t, *J* = 6.6 Hz, 2 H), 3.53 (dd, *J* = 6.3, 6.4 Hz, 2 H), 3.84 (s, 3 H, OCH_3), 5.60 (s, 1 H), 6.84 (dd, *J* = 2.3, 8.8 Hz, 1 H), 6.96 (d, *J* = 2.3 Hz, 1 H), 7.18 (d, *J* = 8.8 Hz, 1 H), 8.50 (s, 1 H, NH).

MS (EI, 70 eV): *m*/*z* (%) = 266 (20), 207 (100), 194 (80), 185 (27), 177 (33), 170 (7), 162 (10), 151 (33), 142 (17), 114 (50), 89 (20).

Anal. Calcd for $C_{13}H_{15}ClN_2O_2$: C, 58.54; H, 5.67; N, 10.50. Found: C, 58.30; H, 5.84; N, 9.35.

***N*-[2-(2-Chloro-5-methoxy-1*H*-indol-3-yl)ethyl]propanamide (Table 1, Entry 6)**

(2-Chloro-5-methoxy-1*H*-indol-3-yl)acetonitrile (**6**; 0.109 g, 0.495 mmol), MeOH (10 mL), propionic anhydride (0.14 mL, 1.1 mmol) and anhyd $NiCl_2$ (0.016 g, 0.12 mmol) were placed into a 30-mL flask. $NaBH_4$ (0.18 g, 4.7 mmol) was added at 0 °C. The mixture was stirred at 25 °C for 4 d, and $NaBH_4$ (0.1 g) was added once per day. When the reaction was complete, the MeOH was evaporated under reduced pressure and the residue was washed with aq K_2CO_3. The product was extracted with EtOAc (2 × 5 mL), and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure; yield: 0.017 g (12%).

^{1}H NMR (400.13 MHz, $CDCl_3$): δ = 1.27 (t, 3 H), 2.12–2.18 (m, 2 H), 3.04 (m, 2 H), 3.68–3.73 (m, 2 H), 3.84 (s, 3 H), 6.83 (d, *J* = 7.1 Hz, 1 H), 6.99 (d, *J* = 7.1 Hz, 1 H), 7.15 (s, 1 H).

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