Aromatization of 1,6,7,7a-Tetrahydro-2*H*-indol-2-ones by a Novel Process. Preparation of Key-Intermediate Methyl 1-Benzyl-5-methoxy-1*H*-indole-3-acetate and the Syntheses of Serotonin, Melatonin, and Bufotenin

Gilbert Revial,[†] Ivan Jabin,[‡] Sethy Lim,[†] and Michel Pfau*,[†]

Laboratoire de Chimie Organique, CNRS (ESA 7084), ESPCI, 10 rue Vauquelin, 75231 Paris Cedex 05, France, and URCOM, Université du Havre, Faculté des Sciences et Techniques, 25 rue Philippe Lebon BP 540, 76058 Le Havre Cedex, France

michel.pfau@espci.fr

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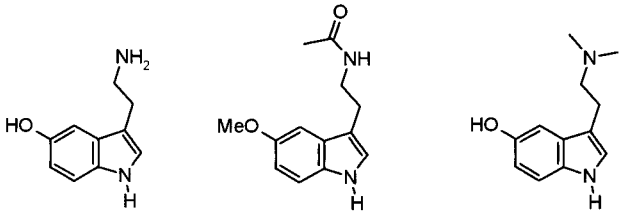
Imine **7** of 1,4-cyclohexanedione mono-ethylene ketal **6** was reacted with maleic anhydride, affording the cyclized adduct **8**. Methyl esterification of **8**, accompanied by transacetalization, led to the dihydrooxindole derivative **10**. Aromatization of **10** was then accomplished with $POCl_3$, leading directly to the key-intermediate title compound **11** in 74% yield from ketone **6**. Serotonin, melatonin, and bufotenin were then obtained by standard reactions.

Introduction

Serotonin **1**, melatonin **2**, and bufotenin **3** are very potent biologically active compounds and several syntheses have been reported:



Serotonin **1** Melatonin **2** Bufotenin **3**

The 5-alkoxytryptamine derivatives are principally synthesized by the Fischer method (e.g., melatonin[1]) or the related Japp−Klingeman/Abramovitch−Shapiro reactions, as well as by the Bischler synthesis. In these methods, the six-carbon atoms ring of the targets is already aromatic in the corresponding starting materials. Alternatively, the syntheses start from a fully aromatic skeleton, either from 5-alkoxyindoles with introduction of the lateral chain (e.g., serotonin,[2,3a] melatonin,[3b] and bufotenin[2a]) or from tryptamine derivatives with introduction of the 5-alkoxy group (e.g., serotonin,[4,5] melatonin,[4,6] and bufotenin[4]).

We report here a new approach for the synthesis of 5-alkoxytryptamine derivatives which involve the synthesis of the corresponding bicyclic skeleton, followed by aromatization.

The Michael addition of imines reacting via their secondary enamines tautomers has been well studied, and many synthetic applications have been described.[7] The reaction has been also extended to enantioselective additions.[8]

One of the first reported reactions concerned the addition of the *N*-cyclohexyl imine of cyclohexanone (**4**) with maleic anhydride leading to compound **5** having the indole-3-acetic acid skeleton[9] (Scheme 1).

Compounds of type **5** appear to be good candidates for the syntheses of tryptamine derivatives. Thus, our syntheses would start with an imine of 1,4-cyclohexanedione mono-ethyleneketal, the reaction of which with maleic anhydride could lead to a compound of type **5** from which the needed functionality in the 5-position could be obtained. Aromatization would then lead to a common

[†] Laboratoire de Chimie Organique, CNRS (ESA 7084).

[‡] URCOM, Université du Havre.

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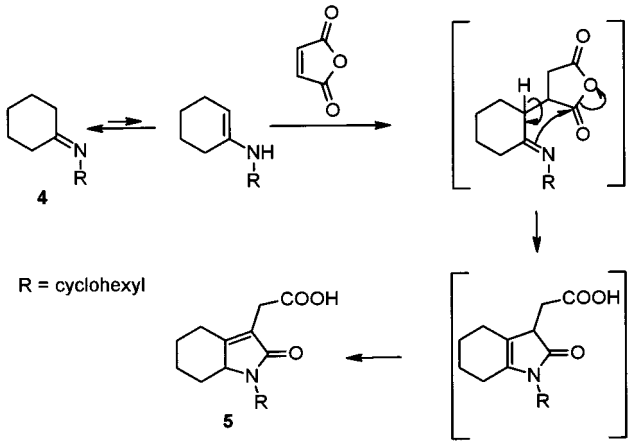
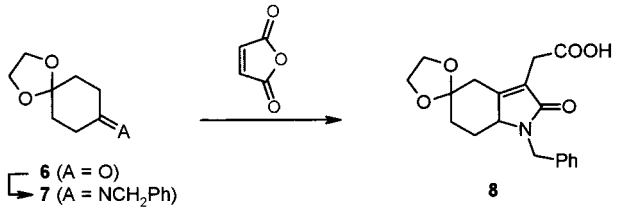
Scheme 1



Scheme 2



intermediate suitable to synthesize either serotonin and melatonin or bufotenin.

Results and Discussion

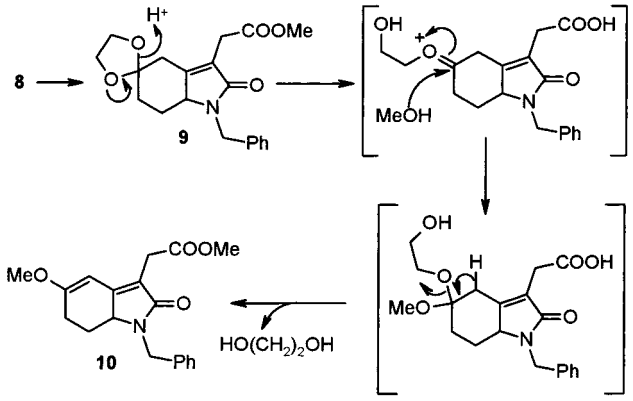
The benzyl imine (**7**) of commercial monoprotected 1,4-cyclohexanedione **6** was reacted with maleic anhydride to afford the crystalline adduct **8** in 96% yield from **6** (Scheme 2).

Ester **9** was readily obtained from acid **8** (90% yield), and it was observed that if the esterification time was extended from 0.5 to 4 h, a transacetalization followed, leading directly to the desired compound **10** in 91% yield from ketone **6** (Scheme 3).

The next step was the aromatization of compound **10**.[10] The reaction of $POCl_3$ is known to transform oxindoles into 2-chloroindoles which in turn can lead to indoles by hydrogenolysis.[11] Thus, ester **10** was reacted with $POCl_3$ and, to our delight, indole **11** was directly obtained in 77% yield. Key-intermediate **11** was also obtained in 74% yield from ketone **6** without purification of the intermediates.

The mechanism proposed for this novel type of aromatization is shown in Scheme 4. Indeed, while HCl elimination is not possible in the case reported above with

Scheme 3



an oxindole, such a process can occur with compound **10**[12] since a CH_2CH_2 moiety is present in the six-atom ring, thus avoiding a hydrogenolysis step.

Further standard reactions from indole **11** led to serotonin **1** and melatonin **2**, as well as to bufotenin **3** (Scheme 5).

Conclusion

We have thus shown that key-intermediate **11**, suited for the preparation of 5-alkoxytryptamine derivatives, can be readily synthesized through a novel aromatization process, in good yield from commercially available ketone **6**.

Experimental Section

General. TLC was performed with glass plates (0.25 mm) precoated with silica gel, and flash chromatography (FC) was carried out with silica gel (200−450 mesh), using EtOAc/hexanes as eluents (proportions given) unless otherwise stated. GC-MS was performed with a HP 5890 GC apparatus (equipped with a 12 m × 0.20 mm dimethylpolysiloxane capillary column) linked to a HP 5971 EIMS. ^1H and ^{13}C NMR spectra of $CDCl_3$ solutions were respectively recorded at 300 and 75.5 MHz. Anhydrous solvents were freshly distilled under argon, CH_2Cl_2 over $CaCl_2$, ether and THF over Na/benzophenone. All reactions were performed under a nitrogen atmosphere. Unless otherwise indicated, after extractions, organic phases were washed with water and brine, dried over $MgSO_4$, filtered, and evaporated under reduced pressure.

***N*-(1,4-Dioxaspiro[4.5]decyl-7-idene)benzylamine (7).** A solution of 3.90 g (25.0 mmol) of commercial 1,4-cyclohexanedione mono-ethylene ketal **6** and 3.00 mL (27.5 mmol) of benzylamine in 25 mL of toluene was heated under reflux in a Dean−Stark apparatus for 6 h. The solvent was removed under reduced pressure affording the crude imine **7** which was directly used for the next step. An analytical sample was obtained by molecular distillation: EIMS *m/z* (rel int) 245 (M^+, 18), 173 (6), 159 (17), 158 (14), 154 (11), 126 (9), 101 (52), 91

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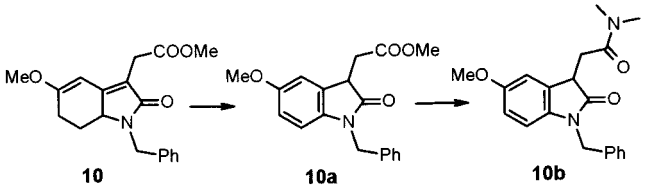
(10) To this end, a preliminary attempt was tried with a first step involving *O*-alkylation of compound **10** with Me_2SO_4 but aromatization of the six-atom ring was observed instead, giving oxindole **10a**, the amidation of which with Me_2NH afforded **10b**.



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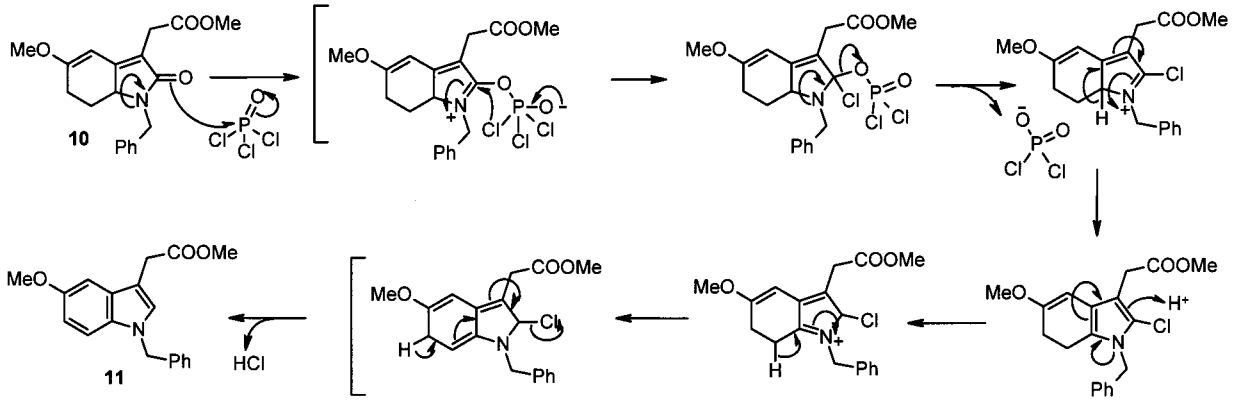
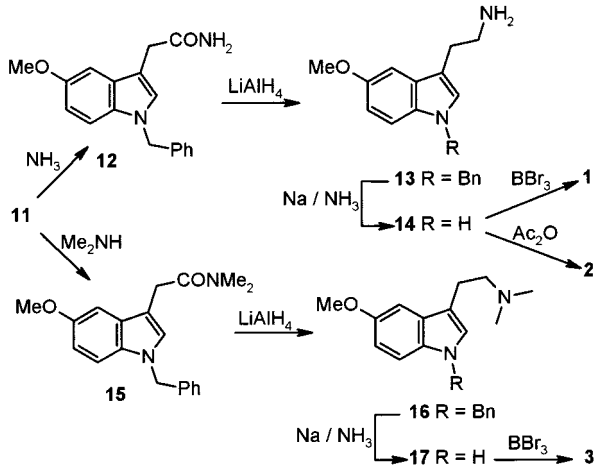
Scheme 4



Scheme 5



(base); ^{1}H NMR (C_6D_6) δ 1.68−1.76 (m, 2H), 1.83−1.90 (m, 2H), 2.32 (dd, J = 7.0, 6.6 Hz, 2H), 2.71 (dd, J = 7.0, 6.6 Hz, 2H), 3.52−3.57 (m, 4H), 4.46 (s, 2H), 7.00−7.47 (m, 5H); ^{13}C NMR (C_6D_6) δ 25.8, 35.2, 35.9, 37.1, 55.1, 64.9 (2C), 108.8, 127−129 (5C), 142.0, 170.7.

1′-Benzyl-2′-oxo-1′,2′,4′,6′,7′,7a′-hexahydrospiro[1,3-dioxolane-2,5′-[5*H*]indole]-3′-acetic Acid (8). A solution of 3.00 g (30.0 mmol, 1.2 equiv) of maleic anhydride in 12 mL of THF was added dropwise to a solution of the crude imine **7** above, in 10 mL of THF at 0 °C. After stirring for 1 h, the crystalline adduct **8** was filtered. Evaporation of the solvent gave a residue which was purified by FC (80:20, then 100:0) affording additional adduct **8**, for a total of 8.25 g (96% yield from **6**). An analytical sample was obtained by recrystallization: mp 199−201 °C (EtOAc/MeOH); calcd for $C_{19}H_{21}NO_5$, C 66.46, H 6.16, N 4.08; found C 66.4, H 6.2, N 4.0; EIMS *m*/*z* (rel int) 299 (M^+ − 44, 10), 297 (25), 210 (13), 99 (38), 91 (base), 65 (14); IR (Nujol) 1715, 1645 cm^{-1}; ^{1}H NMR δ 1.29 (qd, J = 12, 4 Hz, 1H), 1.69 (dt, J = 14, 3.7 Hz, 1H), 1.81 (qd, J = 12, 3 Hz, 1H), 2.18−2.27 (m, 1H), 2.43 (d, J = 14 Hz, 1H), 2.88 (dd, J = 14, 2.6 Hz, 1H), 3.40 (d, J = 15.5 Hz, 1H), 3.47 (d, J = 15.5 Hz, 1H), 3.73 (dd, J = 11.5, 5.8 Hz, 1H), 3.84−4.04 (m, 4H), 4.29 (d, J = 15.1 Hz, 1H), 4.99 (d, J = 15.1 Hz, 1H), 7.30−7.37 (m, 5H), carboxylic H not observed; ^{13}C NMR δ 27.7, 31.9, 32.0, 36.2, 44.5, 60.6, 64.6, 64.9, 109.5, 123.3, 127.9, 128.0 (2C), 128.9 (2C), 136.6, 154.6, 170.7, 172.6.

Methyl 1′-Benzyl-2′-oxo-1′,2′,4′,6′,7′,7a′-hexahydrospiro-[1,3-dioxolane-2,5′-[5*H*]indole]-3′-acetate (9). A mixture of 1.00 g (2.90 mmol) of acid **8**, 3 mL of methanol, 1 mL (3 equiv) of 2,2-dimethoxypropane, and a catalytic amount of PTSA was heated at reflux temperature for 30 min. After evaporation of the solvent and FC (40:60, then 100:0), 0.97 g (90% yield) of oily ester **9** was obtained: HRMS (EI) calcd for $C_{20}H_{23}NO_5$ *m*/*z* 357.1576, found *m*/*z* 357.1579; EIMS *m*/*z* (rel int) 357 (M^+, 7), 326 (2), 312 (1), 297 (1), 99 (base), 91 (34); IR (film) 1736, 1670 cm^{-1}; ^{1}H NMR δ 1.18−1.34 (m, 1H), 1.67 (td, J = 13.6, 3.7 Hz, 1H), 1.74−1.83 (m, 1H), 2.12−2.22 (m, 1H), 2.45 (d, J = 14.3 Hz, 1H), 2.85 (dd, J = 14.3, 2.7 Hz, 1H), 3.31 (d, J = 16.3 Hz, 1H), 3.43 (d, J = 16.3 Hz, 1H), 3.62−3.72 (m, 4H), 3.85−4.02 (m, 4H), 4.26 (d, J = 15.1 Hz, 1H), 4.96 (d, J = 15.1 Hz, 1H), 7.15−7.35 (m, 5H); ^{13}C NMR δ 27.8, 28.7, 32.0, 36.3, 44.1, 51.9, 59.4, 64.4, 64.6, 109.5, 124.3, 127.3, 127.8 (2C), 128.5 (2C), 137.5, 153.2, 170.61, 170.64.

Methyl 1-Benzyl-5-methoxy-2-oxo-2,6,7,7a-tetrahydro-1*H*-indole-3-acetate (10). Crude imine **7** was obtained as above, using in this instance 10.1 g (65.0 mmol) of **6** and 8.00 mL (73.3 mmol) of benzylamine. Its reaction performed as above with maleic anhydride (7.32 g, 74.7 mmol) in 20 mL of THF led to crude acid **8** which was dissolved in a mixture of 200 mL of MeOH, 20 mL of 2,2-dimethoxypropane, and 3.00 g of PTSA. The solution was heated at reflux temperature for 4 h and evaporated. The residue was diluted with EtOAc and washed with a saturated solution of $NaHCO_3$. A FC (80:20) afforded 80 mg of oxindole **10a** (vide infra) and 19.3 g (91% yield from ketone **6**) of viscous ester **10**: HRMS (EI) calcd for $C_{19}H_{21}NO_4$ *m*/*z* 327.1471, found *m*/*z* 327.1468; EIMS *m*/*z* (rel int) 327 (M^+, 51), 312 (5), 296 (5), 268 (21), 267 (29), 252 (13), 195 (11), 194 (14), 176 (20), 91 (base), 77 (7); IR (film) 1735, 1660, 1600 cm^{-1}; ^{1}H NMR δ 1.33−1.50 (m, 1H), 2.11−2.21 (m, 1H), 2.32 (dd, J = 8.5, 3.3 Hz, 2H), 3.33 (d, J = 16.3 Hz, 1H), 3.43 (d, J = 16.3 Hz, 1H), 3.65 (s, 3H), 3.70 (s, 3H), 3.78 (dd, J = 13.0, 4.6 Hz, 1H), 4.39 (d, J = 15.4 Hz, 1H), 4.85 (d, J = 15.4 Hz, 1H), 5.56 (s, 1H), 7.19−7.38 (m, 5H); ^{13}C NMR δ 27.4, 27.7, 28.8, 44.5, 51.9, 55.2, 58.3, 90.7, 116.2, 127.2, 127.7 (2C), 128.4 (2C), 137.9, 152.4, 164.2, 171.1, 172.2.

Methyl 1-Benzyl-5-methoxy-1*H*-indole-3-acetate (11). To a solution of 6.50 g (19.9 mmol) of ester **10** in 22 mL of acetonitrile and 5.3 mL (65.7 mmol, 3 equiv) of pyridine was added dropwise 4.10 mL (44.0 mmol, 2 equiv) of $POCl_3$, and the mixture was stirred at 60 °C for 1 h. After cooling, water was added, and the mixture was extracted with ether. The organic layer was washed with a saturated solution of $NaHCO_3$, followed by the usual workup. A FC (20:80) afforded 5.03 g of oily indole **11** in 82% yield (75% from ketone **6**): HRMS (CI, NH_3) calcd for $C_{19}H_{19}NO_3$ *m*/*z* 309.1365, found *m*/*z* 309.1360; EIMS *m*/*z* (rel int) 309 ($M,^+$ 63), 250 (base), 159 (19), 144 (20), 91 (99); IR (film) 2940, 1740 cm^{-1}; ^{1}H NMR δ 3.68 (s, 3H), 3.73 (d, J = 0.7 Hz, 2H), 3.84 (s, 3H), 5.19 (s, 2H), 6.82 (dd, J = 8.8, 2.2 Hz, 1H), 7.04−7.30 (m, 8H); ^{13}C NMR δ 31.2, 50.2, 51.9, 55.8, 100.9, 106.9, 110.6, 112.2, 126.8 (2C), 127.6, 127.7, 128.3, 128.7 (2C), 131.8, 137.5, 154.1, 172.4.

1-Benzyl-5-methoxy-1*H*-indole-3-acetamide (12). A solution of 6.70 g (21.7 mmol) of indole **11** in 100 mL of MeOH saturated with NH_3 was stirred at room temperature for 8 days, leading to crystalline amide **8**. The suspension was flushed with nitrogen to remove NH_3 and filtered. After washing with MeOH, the crystals were dried over P_2O_5, affording 5.29 g of pure **12** (83% yield[13]): mp 157 °C (MeOH) [lit.[14] 156−157 °C (EtOH)]; calcd for $C_{18}H_{18}N_2O_2$, C 73.45, H 6.16, N 9.52; found C 73.3, H 6.1, N 9.5; EIMS *m*/*z* (rel int) 294 ($M,^+$ 42), 276 (20), 250 (93), 91 (base); IR ($CDCl_3$) 3380,

3140, 1690 cm^{-1}; ^1H NMR δ 3.70 (s, 2H), 3.83 (s, 3H), 5.26 (s, 2H), 5.52 (br s, 1H), 5.69 (br s, 1H), 6.86 (dd, J = 8.8, 2.6 Hz, 1H), 7.00 (d, J = 2.6 Hz, 1H), 7.05 (s, 1H), 7.07−7.14 (m, 2H), 7.18 (d, J = 8.8 Hz, 1H), 7.22−7.35 (m, 3H); ^{13}C NMR δ 33.0, 50.3, 55.9, 100.3, 107.9, 110.9, 112.9, 126.8 (2C), 127.8, 127.9, 128.0, 128.8 (2C), 132.0, 137.2, 154.5, 174.2.

2-(1-Benzyl-5-methoxy-1*H*-indol-3-yl)ethylamine (13). To a suspension of 1.20 g (31.6 mmol) of $LiAlH_4$ in 245 mL of ether was added 2.36 g (8.03 mmol) of amide **12**, and the mixture was heated at reflux temperature for 48 h. After cooling, 5 mL of a 20% solution of potassium sodium tartrate was added dropwise. The aluminum complexes were filtered on Celite and after evaporation of the filtrate, a FC (MeOH/CH_2Cl_2 10:90, then 20:80) afforded 1.36 g (60.5% yield) of oily amine **13**. An analytical sample was obtained by molecular distillation (150 °C/0.02 Torr): calcd for $C_{18}H_{20}N_2O$, C 77.11, H 7.19, N 9.99; found C 77.2, H 7.1, N 9.9; EIMS *m*/*z* (rel int) 280 ($M,^+$ 22), 251 (40), 250 (98), 91 (base); IR (film) 3360, 2930 cm^{-1}; ^1H NMR δ 1.61 (br s, 2H), 2.88 (t, J = 6.6 Hz, 2H), 3.02 (t, J = 6.6 Hz, 2H), 3.86 (s, 3H), 5.23 (s, 2H), 6.83 (dd, J = 8.8, 2.2 Hz, 1H), 6.94 (s, 1H), 7.03−7.15 (m, 4H), 7.20−7.32 (m, 3H); ^{13}C NMR (D_2O) of hydrochloride δ 25.3, 42.3, 52.0, 58.6, 103.8, 111.4, 113.7, 114.1, 129.4 (2C), 130.0, 130.5, 130.9, 131.2 (2C), 134.4, 140.5, 155.8.

2-(5-Methoxy-1*H*-indol-3-yl)ethylamine (5-methoxytryptamine) (14). In 13 mL of THF was condensed at −78 °C ca. 40 mL NH_3, followed by the addition of 0.640 g (28 mmol) of Na (blue color). A solution of 1.30 g (4.60 mmol) of indole **13** in 1 mL of THF was added dropwise, and the mixture was further stirred at −33 °C for 1 h 30. Isoprene was next added dropwise at −50 °C until total discoloration of the mixture occurred, followed by the addition of 1.00 g of NH_4Cl. After NH_3 and solvent evaporation, water was added, and the mixture was extracted with ether (K_2CO_3 drying). A FC (MeOH/EtOAc 50:50 + 5% NH_4OH) afforded 0.580 g (66% yield) of crystalline **14**: mp 122 °C (EtOAc) [lit.[5] 118−120 °C (EtOH), lit.[15] 121.5−122.5 °C (benzene)]; calcd for $C_{11}H_{14}N_2O$, C 69.45, H 7.42, N 14.72; found C 69.5, H 7.4, N 14.8; EIMS *m*/*z* (rel int) 190 ($M,^+$ 32), 161 (75), 160 (base), 145 (22), 117 (10); IR ($CDCl_3$) 3330, 3280, 2920 cm^{-1}; ^1H NMR δ 1.41 (br s, 2H), 2.88 (t, J = 6.6 Hz, 2H), 3.02 (t, J = 6.6 Hz, 2H), 3.85 (s, 3H), 6.85 (dd, J = 8.8, 2.2 Hz, 1H), 6.97 (d, J = 1.5 Hz, 1H), 7.04 (d, J = 2.6 Hz, 1H), 7.21 (d, J = 8.8 Hz, 1H), 8.46 (br s, 1H) [lit.[5] spectrum in agreement with the data reported]; ^{13}C NMR δ 29.4, 42.2, 55.9, 100.7, 111.9, 112.1, 113.2, 123.0, 127.9, 131.7, 153.9.

3-(2-Aminoethyl)-1*H*-indol-5-ol (serotonin) (1). At −78 °C, 2 mL of a BBr_3 (1 M, 2 mmol) solution in CH_2Cl_2 was added dropwise to a solution of 0.100 g (0.630 mmol) of indole **14** in 2 mL of CH_2Cl_2. The mixture was stirred at room temperature overnight and then diluted with water and neutralized with 2.5 M NaOH. The aqueous phase was evaporated and the amorphous solid residue dried over P_2O_5. A FC (MeOH/EtOAc 50:50 + 5% NH_4OH) afforded 0.070 g (65% yield) of serotonin: EIMS *m*/*z* (rel int) 176 ($M,^+$ 22), 147 (50), 146 (base), 117 (7); IR (Nujol) 3480 cm^{-1}; ^1H NMR (DMSO-d_6) δ 2.80 (t, J = 6.8 Hz, 2H), 2.92 (t, J = 6.8 Hz, 2H), 5.45 (br s, 3H), 6.65 (dd, J = 8.8, 2.2 Hz, 1H), 6.87 (d, J = 2.2 Hz, 1H), 7.08 (br s, 1H), 7.17 (d, J = 8.8 Hz, 1H) 10.70 (br s, 1H) [lit.[16] spectrum in agreement with the data reported]; ^{13}C NMR (DMSO-d_6) δ 27.1, 41.2, 102.2, 110.4, 111.4, 111.7, 123.3, 127.8, 130.8, 150.3.

***N*-[2-(5-Methoxy-1*H*-indol-3-yl)ethyl]acetamide (melatonin) (2).** To a solution of 0.590 g (3.10 mmol) of indole **14** in 16 mL of CH_2Cl_2 were added dropwise 1.08 mL (7.8 mmol) of Et_3N and 0.44 mL (4.7 mmol) of Ac_2O. The mixture was stirred at room temperature for 15 min and then extracted with CH_2Cl_2. A FC (80:20, then 100:0) afforded 0.600 g (83% yield) of crystalline melatonin. An analytical sample was obtained through recrystallization: mp 117 °C (toluene/EtOAc) [lit.[3] 116−118 °C (benzene)]; EIMS *m*/*z* (rel int) 232 ($M,^+$ 29), 189 (1), 173 (base), 160 (95), 145 (17); IR ($CDCl_3$) 3280, 2920 cm^{-1}; ^1H NMR δ 1.90 (s, 3H), 2.91 (t, J = 6.8 Hz, 2H), 3.53 (t, J = 6.8 Hz, 1H), 3.57 (t, J = 6.8 Hz, 1H), 3.83 (s, 3H), 5.85 (br s, 1H), 6.84 (dd, J = 8.8, 2.6 Hz, 1H), 6.95 (d, J = 2.2 Hz, 1H), 7.02 (d, J = 2.6 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 8.59 (br s, 1H); ^{13}C NMR δ 23.3, 25.3, 39.8, 55.9, 100.5, 112.1, 112.3, 112.4, 122.9, 127.7, 131.6, 154.0, 170.3 (^1H and ^{13}C NMR spectra identical to those obtained with a commercial authentic sample).

1-Benzyl-5-methoxy-*N*,*N*-dimethyl-1*H*-indole-3-acetamide (15). In a closed vial, a solution of 2.40 g (7.80 mmol) of ester **11** and 19 mg of NaCN in 30 mL of a Me_2NH (10 M) solution in methanol was heated at 50 °C for 4 days. After evaporation of the amine excess and the solvent under reduced pressure, addition of ether brought about the crystallization of amide **15** which was filtered, washed with water and ether, and dried over P_2O_5 (2.50 g, 90% yield). The same reaction carried out with 8.86 g (29.0 mmol) of ester **11** in 76 mL of the Me_2NH solution, at room temperature for 6 days, afforded 9.40 g (91% yield) of amide **15**. An analytical sample was obtained by recrystallization: mp 128 °C (EtOAc); calcd for $C_{20}H_{22}N_2O_2$, C 74.51, H 6.88, N 8.69; found C 74.5, H 6.7, N 8.6; EIMS *m*/*z* (rel int) 322 ($M,^+$ 20), 251 (16), 250 (82), 91 (base); IR (KBr) 3053, 1645 cm^{-1}; ^1H NMR δ 2.96 (s, 3H), 3.01 (s, 3H), 3.78 (s, 2H), 3.85 (s, 3H), 5.22 (s, 2H), 6.85 (dd, J = 9.0, 2.2 Hz, 1H), 7.03 (s, 1H), 7.05−7.15 (m, 4H), 7.20−7.31 (m, 3H); ^{13}C NMR δ 31.3, 35.5, 37.7, 50.0, 55.8, 100.8, 107.8, 110.4, 112.1, 126.6 (2C), 127.2, 127.4, 128.2, 128.6 (2C), 131.7, 137.5, 153.9, 171.4.

2-(1-Benzyl-5-methoxy-1*H*-indol-3-yl)-*N*,*N*-dimethylethylamine (16). The same procedure above for obtaining amine **13** was used with 1.41 g (37.2 mmol) of $LiAlH_4$, 300 mL of ether, and 4.00 g (12.4 mmol) of amide **15**. A FC (EtOH/EtOAc 50:50 + 5% NH_4OH) afforded 3.40 g (90% yield) of oily amine **16**. An analytical sample was obtained by molecular distillation: calcd for $C_{20}H_{24}N_2O$, C 77.89, H 7.84, N 9.08; found C 77.9, H 7.8, N 9.1; EIMS *m*/*z* (rel int) 308 ($M,^+$ 18), 251 (5), 250 (24), 159 (7), 144 (4), 91 (43), 58 (base); IR (film) 1620 cm^{-1}; ^1H NMR δ 2.34 (s, 6H), 2.60−2.69 (m, 2H), 2.87−2.96 (m, 2H), 3.85 (s, 3H), 5.20 (s, 2H), 6.81 (dd, J = 8.8, 2.2 Hz, 1H), 6.91 (s, 1H), 7.05−7.12 (m, 4H), 7.22−7.28 (m, 3H); ^{13}C NMR δ 23.5, 45.5 (2C), 49.9, 55.8, 60.1, 100.9, 110.4, 111.7, 112.8, 126.3, 126.6 (2C), 127.4, 128.4, 128.6 (2C), 131.9, 137.7, 153.7.

2-(5-Methoxy-1*H*-indol-3-yl)-*N*,*N*-dimethylethylamine (17). The same procedure above for obtaining amine **14** was used with 15 mL of THF, ca. 100 mL of NH_3, 1.57 g (68.4 mmol, 6 equiv) of Na, 3.51 g (11.4 mmol) of indole **16** in 15 mL of THF, 2.35 mL of isoprene, and 2 g of NH_4Cl. A FC (MeOH/EtOAc 50/50 + 5% NH_4OH) afforded 2.00 g (80% yield) of crystalline **17**. An analytical sample was obtained by recrystallization: mp 68 °C (cyclohexane); EIMS *m*/*z* (rel int) 218 ($M,^+$ 18), 202 (2) 174 (2), 160 (9), 145 (5), 130 (3), 117 (5), 58 (base); IR (KBr) 1621, 1578 cm^{-1}; ^1H NMR δ 2.35 (s, 6H), 2.60−2.68 (m, 2H), 2.88−2.95 (m, 2H), 3.83 (s, 3H), 6.82 (dd, J = 8.8, 2.6 Hz, 1H), 6.91 (d, J = 2.6 Hz, 1H), 7.03 (d, J = 2.6 Hz, 1H), 7.16 (d, J = 8.8 Hz, 1H), 8.55 (br s, 1H); ^{13}C NMR δ 23.7, 45.4 (2C), 55.9, 60.2, 100.7, 111.9 (2C), 113.7, 122.5, 127.8, 131.6, 153.8.

Picrate of compound 17: mp 177 °C (MeOH); calcd for $C_{13}H_{18}N_2O + C_6H_3N_3O_7$, C 51.01, H 4.73, N 15.66; found C 51.1, H 4.7, N 15.7; ^1H NMR (DMSO-d_6) δ 2.96 (s, 6H), 3.10−3.17 (m, 2H), 3.39−3.48 (m, 2H), 3.88 (s, 3H), 6.85 (dd, J = 8.8, 2.6 Hz, 1H), 7.17 (d, J = 2.6 Hz, 1H), 7.30 (d, J = 2.6 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 8.52 (s, 2H), 9.30 (br s, 1H), 10.91 (s, 1H).

3-[2-(Dimethylamino)ethyl]-1*H*-indol-5-ol (bufotenin) (3). The same procedure above for obtaining serotonin **3** was used with 15 mL of 1 M BBr_3 in CH_2Cl_2 and 1.67 g (7.65 mmol)

(12) To our knowledge, 1,6,7,7a-tetrahydro-2*H*-indol-2-ones of type **10** are not reported in the literature. The generality of the reaction is presently tested in our laboratory with substituted α,β-ethylenic-γ-lactams.

(13) A similar reaction carried out in the presence of 0.1 equiv of NaCN for 24 h at 50 °C gave a comparable yield.

(14) Julia, M.; Igolen, J.; Igolen, H. *Bull. Soc. Chim. Fr.* **1962**, 1060−1068.

(15) Ghosal, S.; Mukherjee, B. *J. Org. Chem.* **1966**, *31*, 2284−2288.

(16) *The Aldrich Library of NMR Spectra*, 2nd ed.; Pouchert, C. J., Ed.; Aldrich Chemical Co., Inc.: St. Louis, 1983.

of indole **17** in 9 mL of CH_2Cl_2. A FC (MeOH/EtOAc 25:75) afforded 0.300 g (23% yield) of amorphous bufotenin: EIMS *m*/*z* (rel int) 204 ($M,^+$ 10), 160 (3), 159 (2), 146 (7), 117 (2), 58 (base); IR (Nujol) 3620 cm^{-1}; ^1H NMR (D_2O) δ 2.76 (s, 6H), 2.95 (t, J = 7.5 Hz, 2H), 3.18 (t, J = 7.5 Hz, 2H), 6.86 (dd, J = 8.8, 2.6 Hz, 1H), 7.02 (d, J = 2.6 Hz, 1H), 7.15 (s, 1H), 7.38 (d, J = 8.8 Hz, 1H); ^{13}C NMR (D_2O) δ 22.9, 45.5 (2C), 60.2, 105.2, 110.4, 114.6, 115.6, 127.8, 129.7, 134.2, 151.5.

Dipicrate of compound 3: mp 178 °C (MeOH) [lit.[15] 177−178 °C (MeOH)]; calcd for $C_{12}H_{16}N_2O + 2\ C_6H_3N_3O_7$, C 43.51, H 3.35, N 16.91; found C 43.8, H 3.3, N 17.4.

Methyl 1-Benzyl-5-methoxy-2-oxo-2,3-dihydro-1*H*-indole-3-acetate (10a). A mixture of 1.50 g (4.70 mmol) of ester **10** and 0.8 mL of Me_2SO_4 in 3 mL of toluene was heated at 90 °C for 45 h. After cooling, neutralization was carried out in an ice bath with dropwise addition of Et_3N. Evaporation of the solvent under reduced pressure was followed by a FC (50:50) affording 0.765 g (50% yield) of viscous oxindole **10a**: EIMS *m*/*z* (rel int) 325 (M^+, 31), 266 (20), 265 (72), 192 (10), 188 (7), 132 (7), 91 (base); IR (film) 1730, 1690 cm^{-1}; ^1H NMR δ 2.78 (dd, J = 16.9, 4.4 Hz, 1H), 3.04 (dd, J = 16.9, 8.1 Hz, 1H), 3.57 (s, 3H), 3.64 (s, 3H), 3.77 (dd, J = 8.1, 4.4 Hz, 1H), 4.80 (d, J = 15.5 Hz, 1H), 4.82 (d, J = 15.5 Hz, 1H), 6.51 (d, J = 8.4 Hz, 1H), 6.59 (dd, J = 8.4, 2.5 Hz, 1H), 6.79 (dd, J = 2.5, 1.1 Hz, 1H), 7.10−7.25 (m, 5H); ^{13}C NMR δ 34.8, 42.1, 43.9, 51.9, 55.6, 109.3, 111.5, 112.2, 127.2 (2C), 127.4, 128.6 (2C), 129.3, 135.8, 136.8, 155.8, 171.2, 176.2.

1-Benzyl-5-methoxy-*N*,*N*-dimethyl-2-oxo-2,3-dihydro-1*H*-indole-3-acetamide (10b). The same procedure above for obtaining amide **15** was used with 0.910 g (2.80 mmol) of ester **10a** and 15 mg of NaCN in 8 mL of the Me_2NH solution with heating for 48 h. The evaporation residue was extracted with EtOAc and a FC (80:20) afforded 0.626 g (66% yield) of crystalline amide **10b**: mp 139 °C (EtOAc/hexane); calcd for $C_{20}H_{22}N_2O_3$, C 70.99, H 6.55, N 8.28; found C 70.9, H 6.6, N 8.3; EIMS *m*/*z* (rel int) 338 ($M,^+$ 24), 266 (53), 265 (base), 188 (12), 91 (22); IR (Nujol) 1700, 1640 cm^{-1}; ^1H NMR δ 2.62 (dd, J = 16.6, 9.6 Hz, 1H), 2.90 (s, 3H), 2.92 (s, 3H), 3.08 (dd, J = 16.6, 2.9 Hz, 1H), 3.64 (s, 3H), 3.94 (dd, J = 9.6, 2.9 Hz, 1H), 4.76 (d, J = 15.4 Hz, 1H), 4.86 (d, J = 15.4 Hz, 1H), 6.49 (d, J = 8.5 Hz, 1H), 6.57 (dd, J = 8.5, 2.6 Hz, 1H), 6.92−6.94 (m, 1H), 7.15−7.24 (m, 5H); ^{13}C NMR δ 34.8, 35.6, 37.0, 42.5, 43.8, 55.6, 109.0, 112.0 (2C), 127.1 (2C), 127.4, 128.6 (2C), 130.7, 135.9, 136.7, 155.7, 169.7, 177.4.

Supporting Information Available: ^1H and ^{13}C NMR spectra of compounds **1**, **2**, **3**, **7**, **8**, **9**, **10**, **10a**, **10b**, **11**, **12**, **13**, **14**, **15**, **16**, **17**; ^1H spectra of the dipicrate of **3**, picrate of **17**. This material is available free of charge via the Internet at http://pubs.acs.org.

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