SYNTHESIS OF ACETAMIDO(INDOL-3-YL)PROPANOL DERIVATIVES

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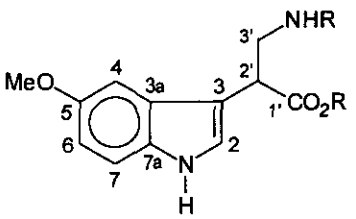
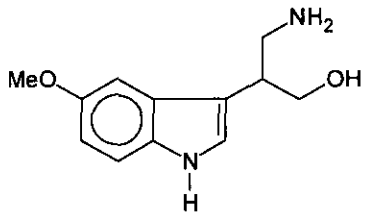
Abstract- A series of acetamido(indol-3-yl)propanol derivatives (**5-7**) has been synthesized using a variety of reductive reactions performed on the corresponding *O*-methyl oximes of an indol-3-yl ester and of several indol-3-yl alcohol derivatives. The *O*-methyl oximes were prepared in good yields by acylation of the corresponding zinc salt of indole, followed by *O*-methyl oximation.

The discovery of the role of serotonin[1] and tryptophan[2] on the central nervous system has been a topic of much interest[3] over several years. This fact has generated significant attention[4] in the search for the synthesis of new structural analogs of these compounds. As a consequence, the synthesis of indorenate (**1**), its amide derivative (**2**), the amido acid (**3**) and the aminopropanol (**4**), which show to possess strong antihypertensive activity,[4] were developed. Later, the synthesis of compounds (**1**) and (**2**) was improved by us.[5] In addition, the inhibition of monoaminooxidase by structural analogs of **4** is well documented.[6]



1: R = H HCl ; R' = Me
2: R = Ac ; R' = Me
3: R = Ac ; R' = H



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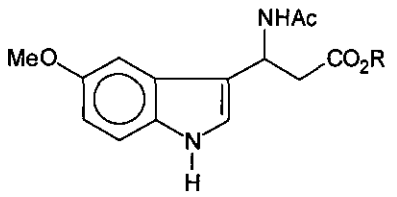
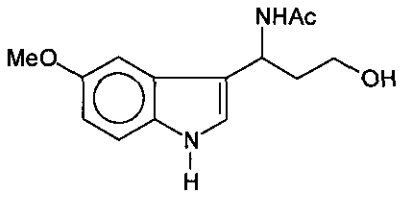
In our search for new drug candidates with similar physiological effect to **1-4** we have prepared the amidoindole derivatives (**5-7**) which have the 5-methoxyindol-3-yl group, originally found at C2 of the side chain in **2-4**, shifted to C3. In the present paper we wish to report the synthesis of acetamido(indol-3-yl)propanol derivatives (**5-7**), in an effort to generate further antihypertensive agents.



5: R = Me
6: R = H



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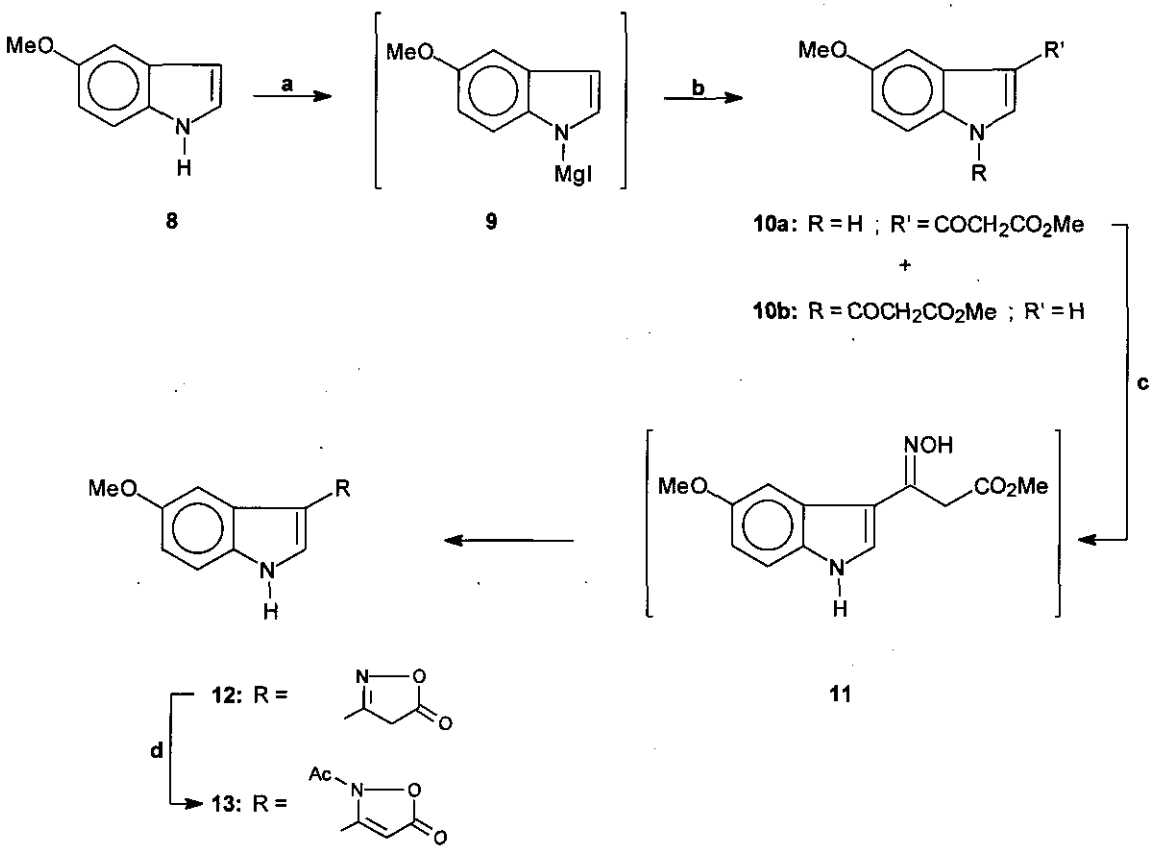
The 1,3-dicarbonyl compound (**10a**), which is used as the starting material, was prepared with high degree of regioselectivity by the directed C3 acylation of the appropriate indole[7] (Scheme 1). Thus, treatment of 5-methoxyindole (**8**) with methylmagnesium iodide afforded the indole Grignard reagent (**9**), which was transmetalated with zinc chloride and then treated with methyl malonyl chloride to give methyl 3-(5-methoxy-1*H*-indol-3-yl)-3-oxopropionate (**10a**) in 56% yield, along with its isomer (**10b**) in 2% yield.

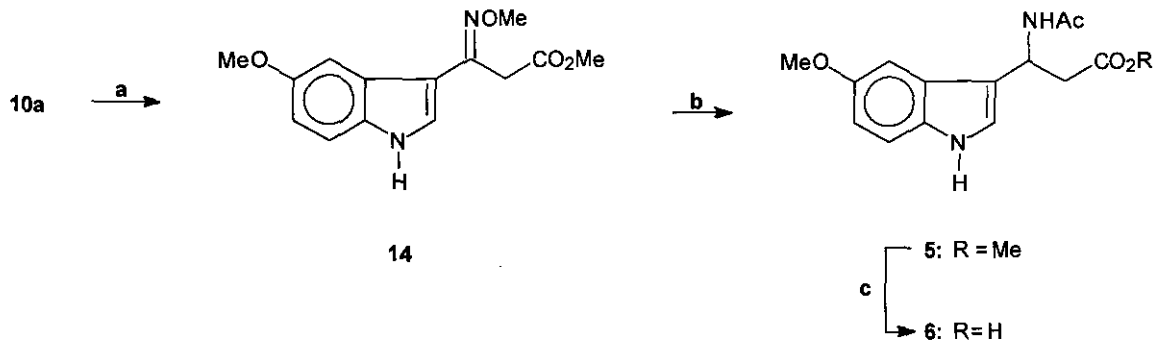


Scheme 1

Reagents and conditions: (**a**) MeMgI, ether, room temperature. (**b**) $ZnCl_2$, methyl malonyl chloride, ether, room temperature. (**c**) $H_2NOH{\cdot}HCl$, EtOH, pyridine, reflux. (**d**) Raney Ni, Ac_2O, H_2/3.4 atm, room temperature.

Previously, **10a** was obtained by Fischer condensation of *p*-methoxyphenylhydrazine hydrochloride with the ethylenedithioketal of 3-oxo-5-oxyaldehyde, followed by deprotection of the keto group in 28% yield.[8] We next studied the reaction of **10a** with hydroxylamine hydrochloride in order to incorporate a potential amino function at the C3 position of the side chain. In the course of the reaction the oxime (**11**) was formed, and spontaneously cyclized[9] *via* intramolecular attack of the oxime functionality on the carbonyl ester group to give the isoxazolone (**12**) in 53% yield. Against our expectation,[10] the scission of the nitrogen-oxygen bound by hydrogenation of **12** in acetic anhydride over Raney Nickel under 3.4 atm of H_2 was unsuccessful, affording only the *N*-acetylated tautomer (**13**) in 28% yield.

Ultimately, the synthesis of **5** and **6** was carried out from **10a** *via* a more confident route (Scheme 2). Treatment of **10a** with methoxylamine hydrochloride in pyridine afforded the *O*-methyloxime (**14**) in 89% yield. Catalytic hydrogenation of **14** in the presence of Raney Nickel in acetic anhydride under 3.4 atm of H_2 provided the desired 3-amido ester (**5**) in 78% yield. Compound (**5**) was further converted into the 3-amido acid (**6**) (93% yield) by hydrolysis with 10% sodium hydroxide in methanol at room temperature. In contrast, when the hydrolysis of **5** was carried out under severe reaction conditions (refluxing in aqueous 10 N NaOH), 5-methoxyindole (**8**) was produced in 73% yield. Probably, compound (**8**) arose from a retro-Michael type condensation.[11]

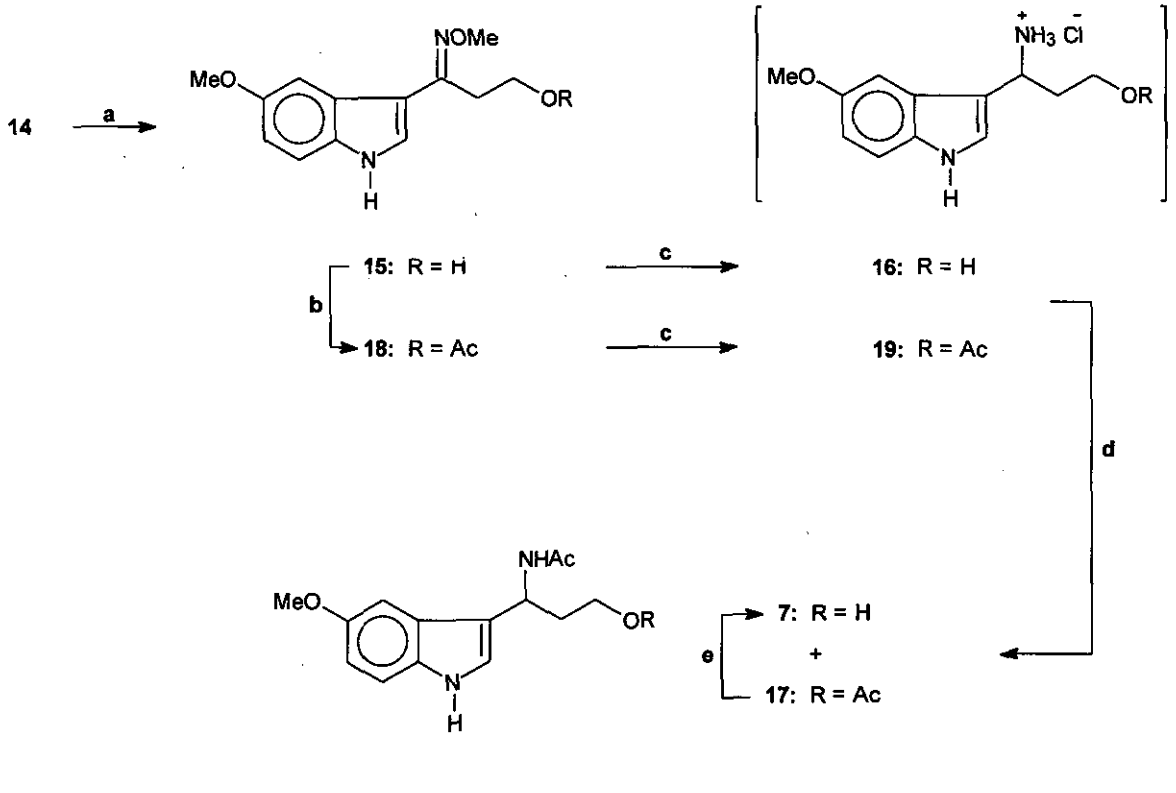


Scheme 2

Reagents and conditions: (**a**) $MeONH_2$·HCl, EtOH, pyridine, room temperature. (**b**) Raney Ni, Ac_2O, H_2/3.4 atm, room temperature. (**c**) NaOH, MeOH/H_2O, room temperature.

Concerning the synthesis of the 3-amidopropanol (**7**) (Scheme 3), we first treated the *O*-methyloxime (**14**) with lithium aluminum hydride in tetrahydrofuran under reflux. The reduction was chemoselective towards the carbonyl group (C=O) in preference to the oxime (C=N)[12] to afford alcohol (**15**) in 72% yield. Catalytic hydrogenation of **15** over 10% palladium on charcoal in a hydrochloric acid-methanol

solution[13] followed by filtration, gave 3-aminopropanol hydrochloride (**16**) which was used without isolation[14] because of its high unstability. Thus, acetylation of the crude reaction mixture with acetic anhydride at room temperature in the presence of pyridine proceeded with high regioselectivity to give the desired 3-amidopropanol (**7**) as a major product (32% yield), accompanied by the diacetate (**17**) (5% yield). Alternatively, **7** was also obtained by conversion of **15** into the acetate (**18**) using acetic anhydride in pyridine (91% yield), followed by hydrogenation over 10% palladium on charcoal in methanol and subsequent acetylation of the resulting unstable hydrochloride salt of the 3-aminoacetate (**19**), as was previously described for **16**, to afford diacetate (**17**) (43% yield), along with **7** (8% yield). Finally, hydrolysis of **17** with 5% potassium hydroxide in methanol at room temperature afforded **7** in 86% yield.

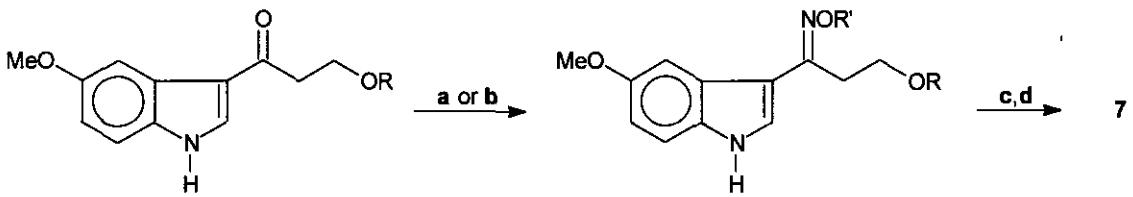


Scheme 3

Reagents and conditions: (**a**) $LiAlH_4$, THF, reflux. (**b**) Ac_2O, pyridine, $CHCl_3$, room temperature. (**c**) 10% Pd/C, MeOH/HCl, H_2/3.4 atm, room temperature. (**d**) pyridine, Ac_2O, 0°C → room temperature. (**e**) KOH, MeOH/H_2O, room temperature.

However, for a larger scale preparation, an alternative efficient route for the synthesis of **7** was still required (Scheme 4). We first examined the reaction of 3-oxopropanol (**20**) and its acetylated derivative

(**21**),[8] with hydroxylamine hydrochloride. Although the oximes (**22**) and (**23**) were isolated in high yields (88 and 94% yield, respectively), they turned out difficult to be used in further transformations because of their low solubility in common organic solvents. Thus, for overcoming this limitation, the preparation of *O*-methyloximes (**15**) and (**18**) was alternatively and independently accomplished by reactions of **20** and **21** with methoxylamine hydrochloride in ethanol under reflux in the presence of pyridine. From these reactions **15** and **18** could be isolated in 84 and 91% yield, respectively. On sequential reductions using Raney Nickel in acetic anhydride under 3.4 atm of H_2 and basic-hydrolysis, the *O*-methyloximes (**15**) or (**18**) furnished the 3-amidopropanol (**7**) in 53% yield.



20: R = H
21: R = Ac

22: R = R' = H
23: R = Ac ; R' = H
15: R = H ; R' = Me
18: R = Ac ; R' = Me

Scheme 4

Reagents: (**a**) $H_2NOH{\cdot}HCl$, EtOH/pyridine, reflux, for **22** and **23**. (**b**) $MeONH_2{\cdot}HCl$, EtOH/pyridine, reflux, for **15** and **18**. (**c**) Raney Ni, Ac_2O, H_2/3.4 atm, room temperature. (**d**) KOH, MeOH/H_2O, room temperature.

EXPERIMENTAL

General Procedure: All experiments dealing with air- and moisture-sensitive compounds were conducted under an atmosphere of dry argon. Anhydrous solvents were dried ($LiAlH_4$) and freshly distilled. All reagents were purchased from the Aldrich Chemical Co. and were used without further purification. Thin layer chromatography was performed on Merck Silica gel 60 plates with fluorescent indicator. Column chromatography was carried out on Merck 60 silica gel 230-400 mesh, unless otherwise noted. Melting points were determined on a Fisher-Johns apparatus and are uncorrected. ^1H and ^{13}C nmr spectra were recorded on a Varian XL-300GS spectrometer at 300 and 75 MHz, respectively. Chemical shifts are expressed in ppm downfield from internal TMS. Splitting patterns are indicated as s, singlet; d, doublet; t,

triplet; q, quartet; m, multiplet; br, broad. Uv spectra was obtained on a Unicam SP-800 spectrophotometer in ethanol solutions. Ir spectra were recorded on a Nicolet MX-1-FT spectrometer. HRms were measured on a Jeol JMS-SX 102A spectrometer. Elemental analyses were performed by the Microanalytical Laboratory Elbach, Germany.

Methyl 3-(5-methoxy-1*H*-3-indolyl)-3-oxopropionate (10a) and methyl 1-(5-methoxy-1*H*-1-indolyl-3-oxopropionate (10b). To a stirred solution of MeMgI (*ca* 7.0 mmol) in dry Et_2O (20 ml) prepared from Mg (173 mg, 7.11 mmol) and MeI (0.44 ml, 7.04 mmol) at room temperature, was added slowly a solution of **8** (1 g, 6.79 mmol) in dry Et_2O (10 ml). The resulting mixture was allowed to stand for 15 min whereafter $ZnCl_2$ (7.13 ml, 43.66 mmol, 1.0 M in Et_2O) was added. The reaction mixture was allowed to stand for further 30 min and methyl malonyl chloride (0.76 ml, 7.10 mmol) in dry Et_2O (10 ml) was added dropwise. The reaction mixture was vigorously stirred for 3 h, quenched with saturated NH_4Cl solution (15 ml) and diluted with AcOEt (120 ml). The organic layer was decanted, washed with saturated $NaHCO_3$ solution (30 ml) followed by brine (2 x 30 ml) and dried over Na_2SO_4. The solvent was removed *in vacuo* and the residual orange solid was crystallized from $CHCl_3$ to give **10a** (762 mg, 45%) as a white solid. The mother liquor was subjected to column chromatography (silica gel 5:1 hexane-AcOEt) to afford in the order of elution, the *N*-acylated isomer (**10b**) (36.7 mg, 2%) as white crystals, and further **10a** (186 mg, 11%).

Compound (10a): mp 143-145 °C ($CHCl_3$); R_f = 0.23 (1:1 hexane-AcOEt) **^{1}H Nmr** ($CDCl_3$) δ 8.86(1H, br s, H-1); 7.89(1H, d, J = 2.6 Hz, H-4); 7.86(1H, d, J = 3.3 Hz, H-2); 7.31(1H, d, J = 9.0 Hz, H-7); 6.93(1H, dd, J = 9.0, 2.6 Hz, H-6); 3.90(2H, s, CH_2); 3.88(3H, s, OCH_3); 3.75(3H, s, CO_2CH_3). **^{13}C Nmr** ($CDCl_3$) δ 186.7(s, C=O); 168.5(s, $\underline{C}O_2CH_3$); 156.7(s, C5); 132.3(d, C2); 131.1(s, C7a); 126.3(s, C3a); 117.3(s, C-3); 114.8(d, C6); 112.2(d, C7); 103.6(d, C4); 55.7(q, OCH_3); 52.5(q, $CO_2\underline{C}H_3$); 47.1(t, CH_2). **Uv** λ_{max} nm(log ε) 216(4.36); 251(4.36); 272(4.24); 302(4.21). **Ir** ν_{max} 3282(NH); 1741 cm^{-1} (C=O). **HRms** *m/z* (M^+) Calcd for $C_{13}H_{13}NO_4$: 247.0845. Found: 247.0837. Anal. Calcd for $C_{13}H_{13}NO_4$: C, 63.15; H, 5.30; N, 5.66. Found: C, 62.89; H, 5.18; N, 5.58.

Compound (10b): mp 117-119 °C (ether/hexane); R_f = 0.63 (1:1 hexane-AcOEt). **^{1}H Nmr** ($CDCl_3$) δ 8.33(1H, br d, J = 9.0 Hz, H-7); 7.33(1H, d, J = 3.8 Hz, H-2); 7.02(1H, d, J = 2.5 Hz, H-4); 6.96(1H, dd, J

= 9.0, 2.7 Hz, H-6); 6.60(1H, dd, J = 3.8, 0.7 Hz, H-3); 3.94(2H, s, CH_2); 3.85(3H, s, OCH_3); 3.79(3H, s, CO_2CH_3). **^{13}C Nmr** ($CDCl_3$) δ 166.6(s, C=O); 163.3(s, NC=O); 156.9(s, C5); 131.5(s, C7a); 130.4(s, C3a); 125.2(d, C2); 117.4(d, C7); 113.7(d, C6); 110.1(d, C3); 103.9(d, C4); 55.6(q, OCH_3); 52.8(q, $CO_2\underline{C}H_3$); 43.3(t, CH_2). **Uv** λ_{max} nm(log ε) 200(4.64); 254(4.55); 304(3.99); 311(3.99). **Ir** ν_{max} 1740, 1700 cm^{-1} (C=O).

3-(5-Methoxy-1*H*-3-indolyl)-4*H*-isoxazolin-5-one (12). To a solution of **10a** (200 mg, 0.81 mmol) in EtOH (4 ml) and pyridine (3 ml) was added $HONH_2$·HCl (250 mg, 3.6 mmol) at once. The reaction mixture was stirred for 3 h under reflux and the excess solvent was removed *in vacuo*. The solid residue was suspended in AcOEt (5 ml), filtered and washed successively with H_2O (3 ml) and acetone (3 ml) to afford **12** (93 mg, 50%) as a white solid, mp 205-207 °C (decomp.) **^{1}H Nmr** (DMSO-d_6) δ 11.77(1H, br s, H-1); 7.83(1H, d, J = 2.9 Hz, H-2); 7.40(1H, d, J = 2.4 Hz, H-4); 7.40(1H, d, J = 8.8 Hz, H-7); 6.87(1H, dd, J = 8.8, 2.4 Hz, H-6); 4.27(2H, s, CH_2); 3.79(3H, s, OCH_3). **^{13}C Nmr** (DMSO-d_6) δ 176.2(s, C=O); 161.3(s, C=N); 154.8(s, C5); 131.5(s, C7a); 131.1(d, C2); 124.0(s, C3a); 113.0(d, C7); 112.8(d, C6); 104.0(s, C3); 102.8(d, C4); 55.2(q, OCH_3); 35.2(t, CH_2). **Uv** λ_{max} nm(log ε) 223(4.25); 255(4.13); 301(3.97). **Ir** KBr ν_{max} 3295 (NH); 1795 cm^{-1} (C=O). **HR**ms *m/z* (M^+) Calcd for $C_{12}H_{10}N_2O_3$: 230.0691. Found: 230.0695.

3-(5-Methoxy-1*H*-3-indolyl)-2-acetyl-2*H*-isoxazolin-5-one (13). To a suspension of **11** (250 mg, 1.01 mmol) in Ac_2O (60 ml) was added Raney Ni W_2 (500 mg), and the resultant mixture was hydrogenated under a H_2 atmosphere at 3.4 atm for 12 h at room temperature and filtered. The filtrate was concentrated *in vacuo* to give a solid residue, which was dissolved in AcOEt (80 ml) and washed with brine (3 x 15 ml). The organic layer was dried over Na_2SO_4, concentrated *in vacuo*, and the residue was purified by column chromatography (silica gel 60-200 mesh, 3:1 hexane-AcOEt, to give **13** (84 mg, 28%) as a white solid, mp 183-185°C (decomp.) **^{1}H Nmr** (DMSO-d_6) δ 11.92(1H, br s, H-1); 7.92(1H, d, J = 3.1 Hz, H-2); 7.40(1H, d, J = 8.8 Hz, H-7); 7.08(1H, d, J = 2.3 Hz, H-4); 6.85(1H, dd, J = 8.8, 2.3 Hz, H-6); 5.99(1H, s, CH); 3.77(3H, s, OCH_3); 2.40(3H, s, $COCH_3$). **^{13}C Nmr** (DMSO-d_6) δ 167.1(s, C=O); 166.4(s, NC=O); 156.0(s, N$\underline{C}$=C); 155.2(s, C5); 132.5(d, C2); 131.1(s, C7a); 126.1(s, C3a); 113.5(d, C7); 112.7(d, C6); 101.9(d, C4); 101.9(s, C3); 90.5(d, CH); 55.7(q, OCH_3); 23.8(q, $CO\underline{C}H_3$). **Uv** λ_{max} nm(log ε) 222(4.52); 252(4.18); 273(3.99); 298(3.89). **Ir** KBr ν_{max} 1758(C=O lactone); 1698 cm-1 (C=O amide).

***O*-Methyl oxime of methyl 3-(5-methoxy-1*H*-3-indolyl)-3-oxopropionate (14).** To a solution of **10a** (300 mg, 1.21 mmol) in EtOH (5 ml) and pyridine (4 ml) was added $MeONH_2$·HCl (350 mg, 4.19 mmol). The reaction mixture was vigorously stirred for 20 h at room temperature and the excess solvent was removed *in vacuo*. The obtained brown solid residue was dissolved in AcOEt (90 ml) and washed successively with 10% aqueous HCl (15 ml) and with water (3 x 15 ml). The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and the solid residue was purified by column chromatography (silica gel 130-270 mesh, 4:1 hexane-AcOEt) to afford **14** (291 mg, 87%) as white crystals. mp 159-161 °C ($CHCl_3$-hexane). **^{1}H Nmr** ($CDCl_3$) δ 11.40(1H, s, H-1); 7.78(1H, d, J = 2.9 Hz, H-2); 7.70(1H, d, J = 2.4 Hz, H-4); 7.31(1H, d, J = 8.8 Hz, H-7); 6.83(1H, dd, J = 8.8, 2.4 Hz, H-6); 3.90(3H, s, $NOCH_3$); 3.78(3H, s, OCH_3); 3.61(3H, s, CO_2CH_3); 3.36(2H, s, CH_2). **^{13}C Nmr** ($CDCl_3$) δ 169.3(s, C=O); 154.2(s, C-5); 149.1(s, C=N); 132.0(s, C7a); 128.2(d, C2); 124.6(s, C3a); 112.2(d, C6); 111.9(d, C7); 111.0(s, C3); 104.8(d, C4); 61.3(q, $NOCH_3$); 55.2(q, OCH_3); 51.6(q, $CO_2\underline{C}H_3$); 32.8(t, CH_2). **Uv** λ_{max} nm(log ε) 224(4.09); 259(4.08); 267(4.14); 290(3.96); 306(3.79). **Ir** ν_{max} 3325(NH); 1735(C=O); 1539 cm^{-1} (C=N). **HRms** *m/z* (M^+) Calcd for $C_{14}H_{16}N_2O_4$: 276.1110. Found 276.1103. Anal. Calcd for $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14. Found: C, 60.62; H, 5.70; N, 10.03.

Methyl 3-acetamide-3-(5-methoxy-1*H*-3-indolyl)propionate (5). A mixture of **14** (200 mg, 0.72 mmol), Raney Ni W_2 (400 mg) in Ac_2O (6 ml) was hydrogenated under a H_2 atmosphere at 3.4 atm for 36 h at room temperature and work-up in a similar manner to that described above for **13**. Purification of the crude product by column chromatography (silica gel 130-270 mesh, 2:1 hexane-AcOEt) afforded **5** (164 mg, 78%) as a white solid, mp 118-120 °C. **^{1}H Nmr** ($CDCl_3$) δ 8.46(1H, br s, H-1); 7.23(1H, d, J = 8.8 Hz, H-7); 7.10(1H, d, J = 2.4 Hz, H-4); 7.05(1H, d, J = 2.4 Hz, H-2); 6.85(1H, dd, J = 8.8, 2.4 Hz, H-6); 6.31(1H, d, J = 8.2 Hz, NHAc); 5.74(1H, ddd, J = 8.2, 7.0, 5.8 Hz, CH); 3.82(3H, s, OCH_3); 3.63(3H, s, CO_2CH_3); 3.01 and 2.94(2H, ABX, J = 15.4, 5.8, 7.0 Hz, CH_2); 1.98(3H, s, $COCH_3$). **^{13}C Nmr** ($CDCl_3$) δ 172.0(s, C=O); 169.5(s, NC=O); 154.2(s, C5); 131.5(s, C7a); 126.2(s, C3a); 122.3(d, C2); 115.2(s, C3); 112.8(d, C6); 112.2(d, C7); 100.7(d, C4); 55.9(q, OCH_3); 51.8(q, $CO_2\underline{C}H_3$); 43.1(d, CH); 39.0(t, CH_2); 23.3(q, $CO\underline{C}H_3$). **Uv** λ_{max} nm(log ε) 222(4.28); 274(3.80); 296(3.65); 307(3.55). **Ir** ν_{max} 3477; 3330(NH); 1731; 1666 cm^{-1} (C=O).

3-Acetamide-3-(5-methoxy-1*H*-3-indolyl)propionic acid (6). To a solution of **5** (200 mg, 0.69 mmol) in MeOH (8 ml) was added aqueous NaOH (10%, 0.75 ml, 1.88 mmol). The reaction mixture was stirred for 3 h at room temperature and the excess solvent was removed *in vacuo*. The residue was diluted with cold water (10 ml) and washed with $CHCl_3$ (20 ml). The aqueous layer was decanted, acidified (pH 3) with 10% aqueous HCl, and extracted with $CHCl_3$ (2 x 20 ml). The combined extracts were washed with brine (2 x 10 ml) and dried over Na_2SO_4. The solvent was removed *in vacuo* to give **6** after crystallization (178 mg, 93%) as white crystals. mp 173-175 °C (decomp.) ($CHCl_3$-hexane). **^{1}H Nmr** (DMSO-d_6) δ 12.13(1H, br s, CO_2H); 10.75(1H, br s, H-1); 8.12(1H, d, J = 7.8 Hz, NHAc); 7.23(1H, d, J = 8.8 Hz, H-7); 7.18(1H, d, J = 2.5 Hz, H-2); 7.07(1H, d, J = 2.4 Hz, H-4); 6.73(1H, dd, J = 8.8, 2.4 Hz, H-6); 5.49(1H, q, J = 7.8 Hz, CH); 3.74(3H, s, OCH_3); 2.80(2H, d, J = 7.8 Hz, CH_2); 1.80(3H, s, $COCH_3$). **^{13}C Nmr** (acetone-d_6) δ 172.6(s, C=O); 169.5(s, NC=O); 154.8(s, C5); 132.8(s, C3a); 123.6(d, C2); 116.7(s, C3); 112.9(d, C7); 112.7(d, C6); 101.8(d, C4); 55.8(q, OCH_3); 43.8(d, CH); 40.2(t, CH_2); 23.0(q, $CO\underline{C}H_3$). **Uv** λ_{max} nm(log ε) 223(4.24); 274(3.79); 297(3.69); 308(3.59). **Ir** ν_{max} KBr 3400(OH); 3335(NH); 1726 cm^{-1} (C=O).

***O*-Methyloxime of 3-(5-methoxy-1*H*-3-indolyl)-3-oxo-1-propanol (15) Procedure A.** To a stirred suspension of $LiAlH_4$ (20 mg, 0.53 mmol) in dry THF (6 ml) under ice-cooling, was added slowly a solution of **14** (100 mg, 0.36 mmol) in dry THF (6 ml). The reaction mixture was heated for 3 h under reflux and then water (5 ml) was added under ice-cooling. The insoluble material that resulted was filtered off. The filtrate was neutralized (pH 7) with 10% aqueous HCl and the THF was evaporated. The residue was extracted with AcOEt (3 x 30 ml). The extract was washed with brine and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the residue was purified by column chromatography (silica gel 60 - 200 mesh, 1:1 hexane-AcOEt) to give **15** after crystallization (65.5 mg, 73%) as pale yellow crystals. mp 104-106 °C ($CHCl_3$). **^{1}H Nmr** ($CDCl_3$) δ 8.61(1H, br s, H-1); 7.86(1H, d, J = 2.5 Hz, H-4); 7.17(1H, d, J = 2.5 Hz, H-2); 7.15(1H, d, J = 8.8 Hz, H-7); 6.86(1H, dd, J = 8.7, 2.5 Hz, H-6); 4.00(3H, s, $NOCH_3$); 3.86(2H, t, J = 6.5 Hz, OCH_2); 3.85(3H, s, OCH_3); 2.96(2H, t, J = 6.5 Hz, CH_2). **^{13}C Nmr** ($CDCl_3$) δ 155.1(s, C5); 153.9(s, C=N); 132.0(s, C7a); 126.4(d, C2); 125.0(s, C3a); 113.1(d, C6); 112.6(s, C3); 111.9(d, C7); 105.1(d, C4); 61.8(q, $NOCH_3$); 60.8(t, OCH_2); 55.8(q, OCH_3); 31.1(t, CH_2). **Uv** λ_{max} nm(log ε) 224(4.22); 257(4.19); 266(4.24); 290(4.05); 306(3.85). **Ir** ν_{max} 3472(OH), 3311(NH); 1538 cm^{-1} (C=N). **HRms** *m/z* (M^+) for $C_{13}H_{16}N_2O_3$: 248.1161. Found: 248.1157. Anal. Calcd for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.50; N, 11.28. Found: C, 62.63; H, 6.38; N, 11.11.

Procedure B. To a solution of **20** (300 mg, 1.4 mmol) in EtOH (5 ml) and pyridine (4 ml) was added $MeONH_2$·HCl (350 mg, 4.19 mmol). The reaction mixture was stirred for 20 h at room temperature, and worked-up in a similar manner to that described above for **14**. Purification of the crude product by column chromatography afforded **15** (285 mg, 84%).

***O*-Methyl oxime of 1-acetyl-3-(5-methoxy-1*H*-3-indolyl)-3-oxopropane (18) Procedure A.** A solution of **15** (100 mg, 0.40 mmol) in $CHCl_3$ (3 ml), pyridine (0.05 ml, 0.62 mmol) and Ac_2O (0.1 ml, 1.06 mmol) was stirred for 12 h at room temperature. The resulting mixture was diluted with $CHCl_3$ (10 ml) and the organic layer was washed successively with 10% aqueous HCl (2 ml), saturated $NaHCO_3$ (5 ml) and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 1:1 hexane-AcOEt) to give **18** (106 mg, 91%) as white crystals. mp 106-107 °C (AcOEt-hexane). **^{1}H Nmr** ($CDCl_3$) δ 8.41 (1H, br s, H-1); 7.87(1H, d, J = 2.6 Hz, H-4); 7.41(1H, d, J = 2.9 Hz, H-2); 7.22(1H, d, J = 8.8 Hz, H-7); 6.90(1H, dd, J = 8.8, 2.6 Hz, H-6); 4.35(2H, t, J = 7.4 Hz, OCH_2); 4.03(3H, s, $NOCH_3$); 3.88(3H, s, OCH_3); 3.07(2H, t, J = 7.4 Hz, CH_2); 2.00(3H, s, $COCH_3$). **^{13}C Nmr** ($CDCl_3$) δ 171.3(s, C=O); 155.2(s, C5); 151.8(s, C=N); 132.0(s, C7a); 126.0(d, C2); 125.1(s, C3a); 113.3(d, C6); 113.1(s, C3); 111.7(d, C7); 105.2(d, C4); 61.9(q, $NOCH_3$); 61.8(t, OCH_2); 55.8(q, OCH_3); 27.5(t, CH_2); 21.0(q, $CO\underline{C}H_3$). **Uv** λ_{max} nm(log ε) 226(4.23); 256(4.22); 266(4.28); 290(4.11); 304(3.93). **Ir** ν_{max} 3314 (NH); 1737(C=O); 1538 cm^{-1} (C=N). **HR**ms *m/z* (M^+) Calcd for $C_{15}H_{18}N_2O_4$: 290.1267. Found: 290.1267. Anal. Calcd for $C_{15}H_{18}N_2O_4$: C, 62.06; H, 6.25; N, 9.65. Found: C, 61.89; H, 6.17; N, 9.56.

Procedure B. To a solution of **21** (500 mg, 1.91 mmol) in EtOH (5 ml) and pyridine (4 ml) was added $MeONH_2$·HCl (350 mg, 4.19 mmol). The reaction mixture was stirred for 20 h at room temperature, and worked-up in a similar manner to that described above for **14**. Purification of the crude product by column chromatography afforded **18** (510 mg, 92%). mp 106-107 °C (AcOEt/hexane).

1-Acetyl- (17) and 3-acetamide-3-(5-methoxy-1*H*-3-indolyl)-1-propanol (7) Procedure A. A mixture of **15** (100 mg, 0.40 mmol), 10% Pd-C (50 mg) in MeOH (6 ml) and one drop of 37% aqueous HCl was hydrogenated under a H_2 atmosphere at 3.4 atm for 24 h at room temperature and filtered. The filtrate indicated by tlc the complete consumption of **15**. To this methanolic solution of the crude hydrochloride

salt of the amino alcohol (**16**) was added pyridine (2.5 ml, 31.0 mmol) and Ac_2O (1 ml, 10.60 mmol) at 0 °C. After stirring for 3 h at room temperature under argon bubbling the reaction mixture was diluted with AcOEt (70 ml) and the organic layer was washed successively with 10% aqueous HCl, saturated $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel, 98:2 CH_2Cl_2-MeOH) to give, in the elution order, the *N*-acylated amido alcohol (**17**) (6 mg, 5%) as a white solid and **7** (34 mg, 32%) as a white solid.

Compound (17): mp 145-146 °C ($CHCl_3$/hexano); R_f = 0.36 (95:5 CH_2Cl_2-MeOH). **^{1}H Nmr** ($CDCl_3$) δ 8.67(1H, br s, H-1); 7.23(1H, d, J = 8.8 Hz, H-7); 7.07(1H, d, J = 2.4 Hz, H-4); 7.03(1H, d, J = 2.6 Hz, H-2); 6.85(1H, dd, J = 8.8, 2.4 Hz, H-6); 6.00(1H, br d, J = 8.5 Hz, NHAc); 5.41(1H, q, J = 7.5 Hz, CH); 4.12(2H, m, OCH_2); 3.81(3H, s, OCH_3); 2.28(2H, m, CH_2); 1.99(3H, s, $COCH_3$); 1.95(3H, s, $NCOCH_3$). **^{13}C Nmr** ($CDCl_3$) δ 170.9(s, C=O); 169.5(s, NC=O); 154.1(s, C5); 131.7(s, C7a); 126.3(s, C3a); 122.4(d, C2); 115.6(s, C3); 112.5(d, C6); 112.2(d, C7); 101.0(d, C4); 61.9(t, OCH_2); 55.9(q, OCH_3); 43.6(d, CH); 33.5(t, CH_2); 23.2(q, $NCO\underline{C}H_3$); 20.9(q, $CO\underline{C}H_3$). **Uv** λ_{max} nm(log ε) 223(4.33); 257(4.06); 273(4.02); 300(3.90); 308(3.90). **Ir** ν_{max} 3477; 3356(NH); 1731 cm^{-1} (C=O). **HR**ms *m/z* (M^+) Calcd for $C_{16}H_{20}N_2O_4$: 304.1423. Found: 304.1436. Anal. Calcd for $C_{16}H_{20}N_2O_4$: C, 63.14 ; H, 6.62; N, 9.20. Found: C, 63.10; H, 6.56; N, 9.13.

Compound (7): mp 136-138 °C ($CHCl_3$-hexano); R_f = 0.15 (95:5 CH_2Cl_2-MeOH). **^{1}H Nmr** ($CDCl_3$) δ 8.36(1H, br s, H-1); 7.28(1H, d, J = 8.7 Hz, H-7); 7.09(1H, d, J = 2.5 Hz, H-2); 6.99(1H, d, J = 2.4 Hz, H-4); 6.88(1H, dd, J = 8.7, 2.4 Hz, H-6); 5.83(1H, d, J = 8.1 Hz, NHAc); 5.49(1H, ddd, J = 11.0, 8.1, 3.7 Hz, CH); 3.83(3H, s, OCH_3); 3.73(2H, m, OCH_2); 2.25 and 1.97(2H, m, CH_2); 2.03(3H, s, $COCH_3$). **^{13}C Nmr** ($CDCl_3$) δ 171.1(s, C=O); 154.3(s, C5); 131.6(s, C7a); 126.4(s, C3a); 122.3(d, C2); 116.1(s, C3); 112.8(d, C6); 112.2(d, C7); 100.7(d, C4); 58.6(t, OCH_2); 56.0(q, OCH_3); 43.0(d, CH); 37.3(t, CH_2); 23.1(q, $CO\underline{C}H_3$). **Uv** λ_{max} nm(log ε) 222(4.26); 275(3.79); 296(3.69); 308(3.61). **Ir** ν_{max} 3479(OH); 3331(NH); 1710 cm^{-1} (C=O). **HR**ms *m/z* (M^+) Calcd for $C_{14}H_{18}N_2O_3$: 262.1317. Found: 262.1307. Anal. Calcd for $C_{14}H_{18}N_2O_3$: C, 64.11; H, 6.92; N, 10.68. Found: C, 63.88; H, 6.76; N, 10.55.

Procedure B: Reduction of **18** (100 mg, 0.34 mmol) was carried out in methanol (6 ml) and one drop of 37% aqueous HCl, under a H_2 atmosphere at 3.4 atm, in the presence of 10% Pd-C for 24 h at room

temperature followed by acetylation of the resulting unstable aminoacetate hydrochloride (**19**) with pyridine (2.5 ml, 31.0 mmol) and Ac_2O (1 ml, 10.60 mmol). The work-up of the reaction mixture was conducted as described above for **7** in Procedure A. Purification of the crude product by column chromatography afforded, in the elution order **17** (45 mg, 43%) and **7** (7 mg, 8%).

Hydrolysis of 17. To a solution of **17** (500 mg, 1.6 mmol) in MeOH (25 ml) was added 5% aqueous KOH (7.5 ml, 6.68 mmol) and the mixture was stirred for 1.5 h at room temperature. After removing the MeOH, the residue was suspended into ice-water, extracted with $CHCl_3$ (2 x 50 ml), washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by column chromatography (silica gel 98:2 CH_2Cl_2-MeOH) to provide **7** (370 mg, 86%).

Oxime of 3-(5-methoxy-1*H*-3-indolyl)-3-oxo-1-propanol (22). To a solution of **20** (500 mg, 2.28 mmol) in EtOH (10 ml) and pyridine (5 ml) was added $HONH_2$·HCl (500 mg, 7.2 mmol). The reaction mixture was stirred for 1 h under reflux, the solvents were evaporated *in vacuo* and the residue was suspended on ice-water. The formed solid was filtrated off, washed with water and dried at 40 °C in a vacuum oven to give **22** (471 mg, 88.2%) as a white solid. mp 190-192 °C. **^{1}H Nmr** (DMSO-d_6) δ 11.21(1H, br s, NOH); 10.51(1H, br s, H-1); 7.64(1H, s, H-2); 7.64(1H, d, J = 2.6 Hz, H-4); 7.28(1H, d, J = 8.8 Hz, H-7); 6.78(1H, dd, J = 8.8, 2.6 Hz, H-6); 4.67(1H, br s, OH); 3.74(3H, s, OCH_3); 3.62(2H, t, J = 7.5 Hz, OCH_2); 2.90(2H, t, J = 7.5 Hz, CH_2). **^{13}C Nmr** (DMSO-d_6) δ 153.8(s, C-5); 152.7(s, C=N); 131.9(s, C7a); 126.9(d, C2); 124.7(s, C3a); 112.4(s, C3); 112.0(d, C7); 111.8(d, C6); 104.2(d, C4); 58.4(t, OCH_2); 55.2(q, OCH_3); 30.9(t, CH_2). **Uv** λ_{max} nm(log ε) 223(4.27); 255(4.26); 263(4.30); 286(4.01); 304(3.84). **Ir** KBr ν_{max} 3411(OH); 3223(NH); 1540 cm^{-1} (C=N).

Oxime of 1-acetyl-3-(5-methoxy-1*H*-3-indolyl)-3-oxopropane (23). To a solution of **21** (500 mg, 1.91 mmol) in EtOH (10 ml) and pyridine (5 ml) was added $HONH_2$·HCl (500 mg, 7.2 mmol). The reaction mixture was stirred for 1 h under reflux and worked-up in a similar manner as described above for **22**, to give **23** (500 g, 95%) as a pale yellow solid. mp 152-154 °C. **^{1}H Nmr** (DMSO-d_6) δ 10.40(1H, br s, H-1); 9.94(1H, br s, NOH); 7.78(1H, d, J = 2.6 Hz, H-4); 7.69(1H, d, J = 2.4 Hz, H-2); 7.32(1H, d, J = 8.8 Hz, H-7); 6.81(1H, dd, J = 8.8, 2.6 Hz, H-6); 4.35(2H, t, J = 7.3 Hz, OCH_2); 3.78(3H, s, OCH_3); 3.14(2H, t, J = 7.3 Hz, CH_2); 1.96(3H, s, $COCH_3$). **^{13}C Nmr** (DMSO-d_6) δ 171.1(s, C=O); 155.7(s, C5); 152.8(s,

C=N); 133.3(s, C7a); 127.2(d, C2); 126.3(s, C3a); 113.9(s, C3); 113.8(d, C6); 112.7(d, C7); 105.8(d, C4); 62.1(t, OCH_2); 55.8(q, OCH_3); 27.3(t, CH_2); 20.9(q, $COCH_3$). **Uv** λ_{max} nm(log ε) 224(4.30); 254(4.25); 262(4.28); 286(4.03); 303(3.85). **Ir** KBr ν_{max} 3410(OH); 3229(NH); 1715(C=O); 1540 cm^{-1} (C=N).

Reduction of 15 and 18 with Raney Ni. A mixture of **15** or **18** (2.0 mmol) and Raney Ni W_2 (1.0 g) in Ac_2O (17 ml) was hydrogenated under a H_2 atmosphere at 3.4 atm for 36 h at room temperature and work-up in similar manners as described above for **13**. Purification of the crude product by column chromatography (silica gel, 1:1 hexane-AcOEt) afforded **17** (380 mg, 62%).

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14. ^{1}H Nmr (MeOD-d_3) δ 7.43(1H, br s, H-2); 7.31(1H, d, J = 8.8 Hz, H-7); 7.24(1H, d, J = 2.2 Hz, H-4); 6.82(1H, dd, J = 8.8, 2.2 Hz, H-6); 4.83(1H, t, J = 7.8 Hz, CH); 3.71 and 3.60(2H, m, CH_2); 2.35(2H, m, OCH_2).

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