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Synthetic Studies on Indole Alkaloids.VII.[1] Effect of the Piperidine Ring Substitution on Intramolecular K^{t}BuO/BF_3.Et_2O Cyclization of *N*-(2-Hydroxyethyl)-2-[1-(phenylsulfonyl)-3-indolyl]piperidines

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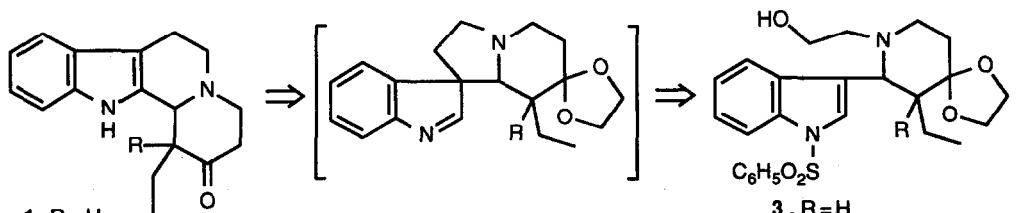
Abstract – 3,3-Disubstituted *N*-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-piperidine **4** shows a particular reactivity in front of K^{t}BuO/BF_3.Et_2O: the intermediate spiroindolenine **15** evolves to a tryptophylpiperidinium salt, which undergoes a Wagner-Meerwein rearrangement followed by a proton elimination to yield the 2,3-disubstituted *N*-tryptophylpiperidine-3-acrylates **19**.

In connection with our studies[2] on the synthesis of *Eburnea* indole alkaloids[3] we have recently described the preparation of 1-ethylindolo[2,3-*a*]quinolizidine **1**, through our usual method to obtain indolo[2,3-*a*]quinolizidin-2-ones, *i.e.*, by K^{t}BuO intramolecular cyclization of protected *N*-(2-hydroxyethyl)-2-[1-(phenylsulfonyl)indolyl]-4-piperidones (**3**), followed by a BF_3.Et_2O induced rearrangement of the intermediate spiroindolenine (Scheme 1).[4]

We report now our studies on the preparation of 1-ethyl-1-(methoxycarbonylmethyl)indolo[2,3-*a*]quinolizidin-2-one (**2**) from the appropriate hydroxyethylpiperidine **4**.

With this purpose, our first aim was to obtain 2-(3-indolyl)piperidine **4**, which was obtained as indicated in Scheme 2, by condensation of 1-(phenylsulfonyl)indole-3-carbaldehyde (**11**)[5] with

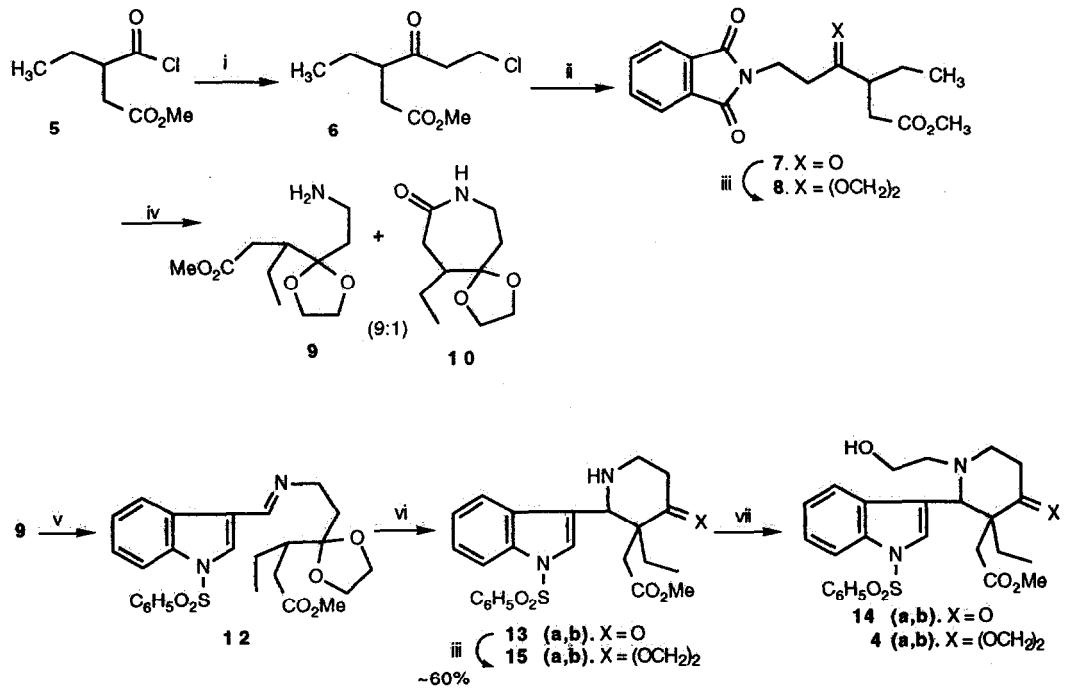


1. R = H
2. R = CH_2CO_2Me
Szántay's intermediate

3. R = H
4. R = CH_2CO_2Me

Scheme 1

the appropriate primary amine **9**, and *p*-TsOH cyclization of the resulting iminoacetal **12**.[6] The primary amine **9** was itself prepared through a Gabriel synthesis starting from the acid chloride **5**.[7] Thus, treatment of **5** with ethylene in the presence of $AlCl_3$ yielded the corresponding chloroethylketone **6**, which was condensed with potassium phthalimide to **7**. Protection of the ketone group was then carried out by treatment of **7** with ethylene glycol in the presence of *p*-TsOH, thus obtaining the desired phthalimidoacetal **8**. Further hydrolysis of the phthalimide was effected with hydrazine hydrate and KOH, which led to the unstable primary amine **9**, accompanied with a small proportion of the seven membered lactam **10** resulting from a lactamization between the ester function and the amine group in the reaction conditions. The most characteristic features of amine **9** in the ^1H NMR spectrum were two singlets at δ 3.90 and 3.65 corresponding to the acetal and the methoxy protons, respectively, the doublet at δ 2.75 due to the acetate methylene group, and the signals at δ 2.19 and 2.40-2.55 assigned to the NCH_2CH_2 moiety. Isolated lactam **10** showed no methoxy signal but a multiplet at δ 3.00-3.15 corresponding to CH_2CON in its ^1H NMR spectrum. The presence of the amide function was also evidenced by the absorption at 1650 cm^{-1} in the IR spectrum, and the structure was confirmed by its mass spectrum (M^+=199) and elemental analysis.



Reagents and conditions: i) CH_2=CH_2, $AlCl_3$, $CHCl_3$, 0°C, 15h (87%); ii) potassium phthalimide, DMF, 115°C, 21h (67%); iii) $(CH_2OH)_2$, *p*-TsOH, C_6H_6, Δ, Dean-Stark, 15h (99%); iv) a. NH_2-NH_2.H_2O, MeOH, Δ, 3.5 h. b. KOH (55%); v) **11**, C_6H_6, 0°C, 30 min; r.t., 2h; Δ, 4h; Dean-Stark, 15h (quant.); vi) dry *p*-TsOH, C_6H_6, Δ, 1 h (83%); vii) $BrCH_2CH_2OH$, K_2CO_3 (1.5 equivalents), EtOH, Δ, 3 days (66%).

Scheme 2

The condensation of crude amine **9** with 1-(phenylsulfonyl)indol-3-carbaldehyde (**11**)[6] led satisfactorily to imine **12**, whose treatment with dry *p*-TsOH led to a 1:1 epimeric mixture on C-3 of piperidone **13**. Thus, piperidones **13** showed carbonyl absorptions at 1737, and 1723 cm^{-1} in the IR spectrum, and no acetal signal at δ~4.0, in the ^1H NMR spectrum. Further significant ^1H NMR spectroscopic data were: i) a doublet (J = 3 Hz) at δ 4.50 (δ 4.30, for isomer **b**) corresponding to 2-H, ii) a singlet corresponding to the methoxy group at δ 3.30 (δ 3.60, for isomer **b**), and iii) a triplet at δ 0.50 due to the methyl group (δ 0.75 for isomer **b**). Similarly the ^{13}C NMR spectrum showed signals at δ 174.4 (*C*OOMe) and 207.1 (CO), δ 57.2 and 57.5 (C-2), and δ 50.9 and 51.09 (OMe). The hydrolysis of the acetal protecting group was rather unexpected since we had never observed it in such Mannich type cyclization reactions. However, this reproducible result could be explained by considering that in this particular case, the greater substitution on C-3 in the piperidine intermediate made the regeneration of the acetal ring difficult.[6] Therefore, in the aqueous work-up the acetal was hydrolyzed.

N-Alkylation of piperidones **13** with 2-bromoethanol in the presence of anhydrous K_2CO_3 led to the corresponding ethanolamines **14**. In order for the alkylation to be complete, long reaction times were required and the quantity of base had to be carefully controlled to avoid the indole deprotection.[8] The incorporation of the alkyl chain was made clear by the presence in the ^{13}C NMR spectrum of the methylene signals at δ 45.0 and 64.0. However, the yield was too low to be synthetically useful, due to the lability of *N*-unsubstituted 4-piperidones which undergo retro-Michael or retro-Mannich reactions in such reaction conditions.

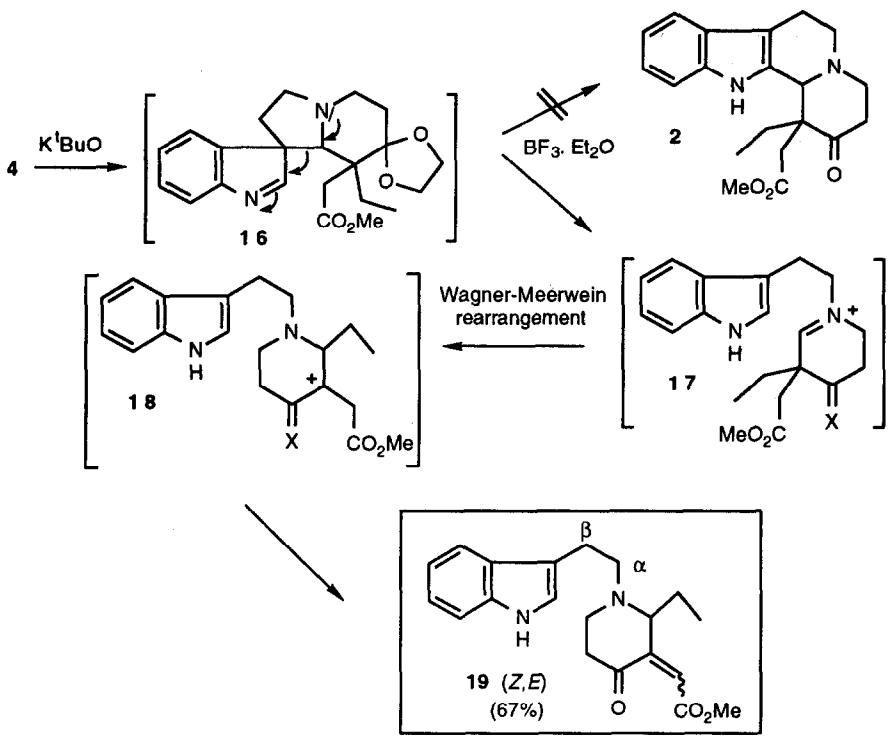
Piperidones **13** were then transformed into the corresponding ethylene acetals **15**. The acetalization yields, never superior to 60%, reflected once again the difficulty of the acetal formation due to the steric hindrance. The most characteristic ^1H NMR data of **15** were the triplets at δ 0.30 and 0.50 (CH_3CH_2), the singlets at δ 3.60 and 3.35 (OMe), and two doublets (J = 2 Hz) at δ 4.30 and 4.35 (2-H) for each epimer respectively, as well as the multiplet at δ 3.85-4.05 (OCH_2), together with a ^{13}C NMR signal at δ 64.1 (acetal).

Piperidine **15** was then alkylated to **4** with 2-bromoethanol in the presence of anhydrous K_2CO_3. The insertion of the 2-hydroxyethyl chain was made clear particularly by the presence in the ^{13}C NMR spectrum of dedoubled methylene signals at δ~49 and δ~63 corresponding to NCH_2 and CH_2OH, respectively for the two C-3 epimers.

With 1-(2-hydroxyethyl)-4-piperidone ethylene acetal (**4**) in hand, we undertook the study of its behaviour with K^{t}BuO (Scheme 3). Thus, from the reaction of **4** with 2 equivalents of K^{t}BuO in THF in our usual reaction conditions (0°C, 30 min) followed by the addition of $BF_3.Et_2O$ (2 equivalents) two compounds were isolated, which were identified as *Z*- and *E*-**19** from their spectral data and elemental analysis. The most characteristic signals in the ^1H NMR spectra of each isomer of **19** were: i) an olefinic proton at δ 6.87 (isomer *E*) (δ 6.50 for *Z*-**19**); ii) two triplets at δ 3.50 (3.55 for isomer *Z*) and δ 2.99 (2.75 for isomer *Z*) corresponding to the piperidine 6-H and 5-H, respectively; iii) two triplets at δ 3.36 (3.05 for isomer *Z*) and δ 2.39 (2.45 for isomer *Z*) assigned to α-H and β-H respectively; iv) a triplet at δ 3.43 (3.40 for *Z*-**19**) corresponding to 2-H. Signal assignments for acrylates **19** were corroborated with 2D NMR experiments.

This result is very interesting since it can only be explained by considering that the intermediate spiroindolenine **16** evolved by a ring opening with anchimeric assistance of the nitrogen atom electron lone pair, as do the 3-monosubstituted analogs,[2] to give the corresponding iminium salt **17**. In 3-monosubstituted cases, the iminium salt evolves either to a lactam by oxidation, or to an enaminone by acetal hydrolysis in the aqueous work-up. However, these exits are not possible in 3,3-disubstituted examples such as ours, due to the lack of a proton on C-3. The iminium salt evolves then by a Wagner-Meerwein rearrangement of the ethyl group to generate a tertiary carbocation which stabilizes itself by a proton elimination reaction leading to a stable acrylate. Simultaneously, the hydrolysis of the acetal function takes place in the aqueous work-up, resulting in the double conjugation of the double bond.

The influence of the C-3 piperidine ring substitution in the $K^tBuO/BF_3.Et_2O$ reaction is therefore clearly demonstrated with this result.



Scheme 3

EXPERIMENTAL

General. Melting points were determined in a capillary tube on a Büchi apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian Gemini-200 spectrometer using TMS as the internal standard. Chemical shifts are reported in ppm (δ)

downfield from TMS. IR spectra were registered with a Nicolet-FT spectrophotometer and only noteworthy absorptions are listed. Mass spectra were determined on a Hewlett-Packard 5930A mass spectrometer. Tlc was carried out on SiO_2 (silica gel 60, Alugram®, Macherey-Nagel), and the spots were located with UV light, iodine or iodoplatinate reagent. Flash column chromatography was carried out on SiO_2 (silica gel 60, 0.040-0.060 mm, SDS). Drying of organic extracts during the workup of reaction mixtures was performed over anhydrous sodium sulphate. Microanalyses were performed on a Carlo-Erba 1106 analyzer by the Departament de Química Orgànica Biològica (CSIC), Barcelona.

Methyl 6-Chloro-3-ethyl-4-oxohexanoate (6). To a dispersion of $AlCl_3$ (8.4 g, 62.7 mmol) in dry $CHCl_3$ (250 ml) freshly distilled (86-87°C, 1mmHg) 2-(methoxycarbonylmethyl)butanoyl chloride[7] (5.6 g, 31.3 mmol) was slowly added under vigourous mechanical stirring at 0°C, and a gentle current of ethylene was passed through the mixture for 6h, maintaining the temperature at 0°C. The reaction mixture was poured on ice-aqueous 10% HCl, and extracted with $CHCl_3$. The organic extracts were washed with aqueous 10% $NaHCO_3$, dried, and evaporated to yield chloroester **6** (5.57g, 87%) as a colorless oil, which was used without further purification: IR (NaCl) 1770 (CO), 1720 cm^{-1} (COOMe); ^1H NMR 0.90 (t, J = 7 Hz, 3H, CH_3CH_2), 1.40-1.70 (m, 2H, CH_2CH_3), 2.88 (d, J = 7 Hz, 2H, CH_2COOMe), 2.90 (t, J = 7 Hz, 2H, CH_2CO), 3.05 (t, J = 7 Hz, 2H, CH_2Cl), 3.65 (s, 3H, OCH_3); ^{13}C NMR 10.7 (CH_3CH_2), 24.4 (CH_3CH_2), 37.7 ($COCH_2$), 40.7 (CH), 43.5 (CH_2COOMe), 44.6 (CH_2Cl), 51.2 (OMe), 175.3 (COOMe), 205.6 (CO); MS (*m/z*, %) 207 (M^+, 2), 188 (1), 175 (21), 143 (71), 139 (4), 116 (13), 115 (44), 101 (100), 91 (77). Anal. Calcd for $C_9H_{15}ClO_3$: C, 52.30; H, 7.32; Cl, 17.15. Found: C, 52.30; H, 7.26; Cl, 17.51.

Methyl 3-Ethyl-4-oxo-6-phthalimidohexanoate (7). A solution of chloride **6** (7 g, 33.9 mmol) and potassium phthalimide (6.9 g, 37.3 mmol) in dry DMF (70 ml) was stirred at 115°C for 15 h under N_2 atmosphere. The reaction mixture was poured on ice-water and extracted with CH_2Cl_2. The organic extracts were washed with 10% aqueous Na_2CO_3, dried and evaporated furnishing a brown solid which was flash chromatographied (Et_2O), thus obtaining pure **7** (7.62 g, 71%): mp 89°C (acetone); IR ($CHCl_3$) 1760, 1740-1680 cm^{-1} (CO); ^1H NMR 0.90 (t, J = 7 Hz, 3H, CH_2CH_3), 1.40-1.70 (m, 2H, CH_2CH_3), 2.90 (t, J = 7 Hz, 2H, CH_2CO), 3.00 (t, J = 7 Hz, 2H, CH_2N), 3.66 (s, 3H, OMe), 7.60-7.90 (2m, 4H, Ar-H); ^{13}C NMR 10.9 (CH_3CH_2), 24.5 (CH_3CH_2), 32.4 (CH_2CO), 40.3 (CH_2N), 40.8 (CH), 51.36 (OMe), 123.0 (C-*o*), 131.8 (C-*i*), and 133.9 (C-*m*), 167.9 (COOMe), 172.3 (CO), 175.2 (CO imide); MS (*m/z*, %) 317 (M^+, 1), 299 (0.5), 286 (7), 285 (6), 217 (17), 202 (32), 174 (13), 160 (100). Anal. Calcd for $C_{17}H_{19}NO_5$: C, 64.34; H, 6.03; N, 4.41. Found: C, 64.18; H, 6.03; N, 4.44.

Methyl 3-Ethyl-4,4-ethylenedioxy-6-phthalimidohexanoate (8). A mixture of phthalimidoketone **7** (1.5 g, 4.7 mmol), *p*-TsOH.H_2O (90 mg, 0.47 mmol) and ethylene glycol (0.26

ml, 5.8 mmol) in dry benzene (50 ml) was refluxed for 15 h with a Dean-Stark trap. The reaction mixture was poured on ice-water and the layers separated. The organic phase was washed with 10% aqueous Na_2CO_3, dried and evaporated to yield phthalimidoacetal **8** (1.85 g, 98%) as an oil: IR ($CHCl_3$) 1710-1700 cm^{-1} (CO imide); ^1H NMR 0.89 (t, *J*= 7 Hz, 3H, CH_3CH_2), 1.40-1.65 (m, 3H, CH and CH_2CH_3), 1.75 (dd, *J* = 12, 2 Hz, 1H, CH_ACO_2Me), 2.00 (t, *J*=7 Hz, NCH_2CH_2), 2.20 (t, *J*=12 Hz, 1H, CH_BCO_2Me), 3.60 (s, 3H, OMe), 3.75 (t, *J*=7 Hz, 2H, NCH_2), 3.90 (s, 4H, OCH_2), 7.65-7.72 and 7.72-7.90 (2m, 4H, Ar-H); ^{13}C NMR 11.3 (CH_3CH_2), 26.3 (CH_3CH_2), 33.1 (CH_2COO), 64.6 (OCH_2), 109.2 (OCO), 123.0 and 133.8 (Ar-C), 167.9 (COOMe), 176.3 (CO imide); MS (m/z, %) 361 (M^+, 0.1), 330 (2), 302 (2), 286 (4), 285 (6), 258 (7), 246 (53), 217 (23), 202 (13), 187 (48), 174 (17), 160 (100), 143 (15), 133 (14), 130 (20), 99 (93). Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.87. Found: C, 63.01; H, 6.10; N, 3.88.

Methyl 6-Amino-3-ethyl-4,4-ethylenedioxyhexanoate (9). To a solution of phthalimide **8** (3 g, 8.3 mmol) in MeOH (50 ml), 80% NH_2-$NH_2.H_2O$ (0.6 ml, 12.4 mmol) was added and the mixture was refluxed for 3h. The solvent was distilled under atmospheric pressure and the resulting residue was dissolved in 2.6 *N* KOH and CH_2Cl_2.The layers were separated and the aqueous phase extracted with CH_2Cl_2. The organic extracts were dried and the solvent removed by distillation under atmospheric pressure to give amine **9** (1.05 g, 55%, calculated from the ^1H-NMR integration of the residue) as a pale oil, which was directly used in the following reaction. The spectra also showed the presence of a small quantity (9:1) of 4-ethyl-5,5-ethylenedioxy-2-oxoazepine (**10**). Amine **9** (from the mixture): IR (NaCl) 3400 (NH_2), 1720 cm^{-1} (CO_2Me); ^1H NMR 0.85 (t, *J*=7 Hz, 3H, CH_2CH_3), 1.60-1.90 (m, 3H, CH_2CH_3 and CH), 2.19 (t, *J*=12 Hz, 2H, NCH_2CH_2), 2.40-2.55 (m, 2H, NCH_2), 2.75 (d, *J*=12 Hz, 2H, CH_2CO_2Me), 3.65 (s, 3H, OMe), 3.90 (s, 4H, OCH_2), 7.20 and 7.40 (2 br s, NH); ^{13}C NMR 11.7 (CH_3CH_2), 26.3 (CH_2CH_3), 36.7 (CH_2CO_2Me), 38.8 (NCH_2CH_2), 39.2 (NCH_2), 42.0 (CH), 51.1 (OMe), 64.6 (OCH_2), 108.8 (OCO), 179.6 (CO); MS (*m/z*, %) 231 (M^+, 0.3), 217 (1), 215 (1), 187 (47), 171 (13), 154 (11), 140 (27), 127 (64), 99 (100).

A sample (300 mg) of the mixture was flash chromatographied (90:10, CH_2Cl_2-MeOH) to isolate lactam **10** as a white solid: mp 115-117°C; IR ($CHCl_3$) 3400 (NH), 1650 cm^{-1} (CO amide); ^1H NMR 0.95 (t, *J*=7 Hz, 3H, CH_3CH_2), 1.00-1.35 (m, 2H, CH_2CH_3), 1.50-2.00 (m, 2H, NCH_2CH_2), 2.30-2.50 (m, 1H, CH), 3.00-3.15 (m, 2H, CH_2CO), 3.20-3.50 (m, 2H, NCH_2), 3.90 (s, 4H, OCH_2), 6.80 and 7.00 (2 br s, NH); ^{13}C NMR 11.8 (CH_3CH_2), 24.1 (CH_3CH_2), 36.9 (C-6), 38.8 (C-4), 39.0 and 39.3 (C-3 and C-7), 64.4 and 64.6 (OCH_2), 108.5 (C-5), 179.1 (CO); CIMS (*m/z*) 234 (M^++35), 217 (M^++15), 200 (M^++1), 136. Anal. Calcd for $C_{10}H_{17}NO_3$: C, 60.28; H, 8.74; N, 7.03. Found: C, 60.24; H, 8.73; N, 6.89.

3-Ethyl-3-(methoxycarbonylmethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidone (13). To a solution of crude amine **9** (1.06 g, 4.58 mmol) in dry C_6H_6 (100 ml) cooled at 0°C, 1-phenylsulfonyl-3-indolecarbaldehyde[5] (1.43 g, 5.0 mmol) was added portionwise. The resulting

solution was stirred at 0°C for 30 min, at room temperature for 1 h, and under reflux for 4 h. Then a Dean-Stark trap was settled and the reflux was left for 15 h. The solvent was evaporated to yield **methyl 3-ethyl-4,4-ethylenedioxy-6-[1-(phenylsulfonyl)-3-indolylmethyleneimino]-hexanoate (12)** (2.77 g, 99%) which was used without further purification: IR (Nujol): 1732 (CO_2Me), 1680 cm^{-1} (imine); ^1H NMR (60 MHz) 1.05 (t, J=7 Hz, 3H, CH_3CH_2), 3.70 (s, 3H, OMe), 4.00 (s, 4H, OCH_2), 7.20-7.50, 7.70-8.00 and 8.10-8.30 (3 m, Ar-H), 10.05 (s, HC=N).

A solution of p-TsOH.H_2O (1.75 g, 9.24 mmol) in C_6H_6 (80 ml) was refluxed with a Dean-Stark trap for 3 h. A solution of iminoacetal **12** (2.3 g, 4.61 mmol) in dry C_6H_6 (60 ml) was then slowly added, and the resulting solution was stirred under reflux for 1 h. The cooled reaction mixture was poured upon ice-water, and basified with $NaHCO_3$. The layers were separated and the organic phase was washed with aqueous $NaHCO_3$, dried and evaporated to give an oil which was flash chromatographied (97:3, CH_2Cl_2-MeOH) to furnish piperidone **13** as a 1:1 epimeric mixture on C-3 (oil, 1.73 g, 83%): IR ($CHCl_3$) 3400 (NH), 1737, 1721, 1713 cm^{-1} (CO); ^1H NMR 0.50* and 0.75 (2t, J=7Hz, 3H each, CH_3CH_2), 1.10-1.40 (m, CH_ACH_3), 1.55-1.95 (m, CH_BCH_3), 2.05 (br s, NH), 2.20 (td, J=7, 2 Hz, 5-Ha), 2.40-2.65 (m, 5-He and CH_2CO_2Me), 2.95-3.15 (m, 6-H), 3.30* and 3.60 (2 s, 3H each, OMe), 4.30 and 4.50* (2 d, J=3 Hz, 1H each, 2-He), 7.20-7.60 and 7.70-8.05 (Ar-H); ^{13}C NMR 12.2 and 12.4 (CH_3CH_2), 21.9 and 22.1 (CH_3CH_2), 42.2 (CH_2CO_2Me), 43.5 (C-5),44.9 (C-6), 50.9 and 51.1 (OMe), 57.2 and 57.5 (C-2), 113.7 (In-C7), 121.0 (In-C5), 123.3 (In-C4), 124.6 (In-C6), 125.1 (In-C2), 126.8 (C-o), 129.3 (C-m), 134.0 (C-p), 137.9 (C-i), 174.4 (CO_2Me), 207.1 (CO); MS (m/z, %) 454 (M^+, 30), 425 (50), 395 (74), 352 (16), 171 (17), 157 (23), 84 (100). The hydrochloride (**13**.HCl) melted at 149-151°C (acetone-Et_2O). Anal. Calcd for $C_{24}H_{26}N_2O_5S$.HCl: C, 58.71; H, 5.54; N, 5.70. Found: C, 58.47; H, 5.55; N, 5.58.

3-Ethyl-1-(2-hydroxyethyl)-3-(methoxycarbonylmethyl)-2-[1-(phenylsulfo-nyl)-3-indolyl]-4-piperidinone (14). To a solution of piperidones **13** (490 mg, 0.98 mmol) in absolute MeOH (50 ml) and dry CH_2Cl_2 (0.5 ml, to complete the solubilization), K_2CO_3 (200 mg, 1.47 mmol), and 2-bromoethanol (0.14 ml, 1.97 mmol) were added. The mixture was refluxed for 24 h and the solvent was evaporated. The residue was dissolved in H_2O-CH_2Cl_2, the layers were separated and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were dried and evaporated to yield an oil which was flash chromatographied (98:2, CH_2Cl_2-MeOH) to obtain **14** (39 mg, 8%) as an epimeric mixture on C-3: IR (NaCl) 3600-3200 (OH), 1737, 1713 cm^{-1} (CO); ^1H NMR 0.35* and 0.60 (2 t, J=7 Hz, 3H each, CH_3CH_2), 0.75-1.00 (m, CH_2CH_3), 1.05-1.40 (m, CH_2CO_2Me), 1.50-1.90 (m, 5-H), 1.90-2.15 (m, NCH_ACH_2O), 2.40-2.90 (m, NCH_BCH_2O), 3.00-3.20 (m, 6-H), 3.30 and 3.70* (2 s, 3H each, OMe), 3.55-3.80 (m, CH_2OH), 3.85* and 4.25 (2t, J=2 Hz, 1H each, 2-H), 7.10-7.60 and 7.65-8.10 (m, Ar-H); ^{13}C NMR 12.1 (CH_3CH_2), 22.1 (CH_3CH_2), 40.5 and 41.1 (C-5), 43.0 (CH_2CO_2Me), 45 (NCH_2), 50.1 and 51.9 (OMe), 55.5 (C-6), 59.3 (C-2), 64.4 (CH_2OH), 114.3 (In-C7), 123.8 (In-C4), 125.5 (In-C6 and In-C5), 126.8 (C-o), 129.4 (C-m), 134.1 (C-p), 174.5 (CO); MS (m/z, %) 498 (M^+, 2), 470 (11), 467 (M^+-CH_2OH, 15), 395 (8), 297

* Stars indicate data of the same isomer.

(20), 236 (32), 208 (16), 182 (15), 167 (18), 77 (100). Anal. Calcd for $C_{26}H_{30}N_2O_6S.H_2O$: C, 60.44; H, 6.24; N, 5.42. Found: C, 60.42; H, 6.17; N, 5.32.

3-Ethyl-3-(methoxycarbonylmethyl)-2-[1-(phenylsulfonyl)-3-indolyl]-4-piperidone Ethylene Acetal (15). Operating as in the preparation of phthalimidoacetal **8**, from piperidones **13** (213 mg, 0.47 mmol), *p*-TsOH (133.8 mg, 0.09 mmol), and ethylene glycol (80 µl, 1.42 mmol) in dry C_6H_6 (30 ml), piperidine acetal **15** was obtained (135 mg, 57%) after flash chromatography (97:3, CH_2Cl_2-MeOH): mp 128°C (acetone-Et_2O); IR (NaCl) 3350 (NH), 1732 cm^{-1} (CO_2Me); ^1H NMR 0.30* and 0.50 (2 t, *J*=7 Hz, 3 H each, CH_3CH_2), 1.00-1.40 (m, CH_3CH_2), 1.50-1.90 (m, 5-H), 2.00-2.20 (m, 6-Ha), 2.25-2.65 (m, CH_2CO_2Me), 2.85-3.15 (m, 6-He), 3.35 and 3.60* (2 s, 3H each, OMe), 3.85-4.05 (m, OCH_2), 4.30* and 4.35 (2 d, *J*= 2Hz, 1H each, 2-H), 7.20-7.55 (m, Ar-H), 7.60 (d, *J*=2 Hz, In-2H), 7.70-8.05 (2 m, Ar-H); ^{13}C NMR 13.66 (CH_3CH_2), 21.3 (CH_3CH_2), 35.1 (C-5), 43.6 (CH_2CO_2Me), 44.6 (C-6), 50.9 (C-2), 55.0 (OMe), 63.6 and 64.3 (OCH_2), 109.0 (C-4), 113.7 (In-C7), 121.3 (In-C5), 123.3 and 123.4 (In-C4), 124.9 and 129.3 (In-C6), 126.8 (C-*o*), 129.3 (C-*m*), 133.9 (C-*p*), 135.4 and 138.2 (C-*i* and In-C7a), 174.7 and 175.2 (CO_2Me). MS (*m/z*, %) 498 (M^+, 8), 469 (15), 453 (34), 440 (15), 397 (47), 357 (100), 312 (17), 297 (54), 283 (46), 187 (69). Anal. Calcd for $C_{26}H_{30}N_2O_6S$: C, 62.63; H, 6.06; N, 5.62. Found: C, 62.23; H, 6.49; N, 5.84.

3-Ethyl-1-(2-hydroxyethyl)-3-(methoxycarbonylmethyl)-2-[1-(phenylsulfo-nyl)-3-indolyl]-4-piperidone Ethylene Acetal (4). A mixture of piperidine acetals **15** (305 mg, 0.61 mmol), K_2CO_3 (127 mg, 0.92 mmol), and 2-bromoethanol (90 µl, 1.22 mmol) in absolute MeOH (50 ml) was refluxed for 3 days. The solvent was evaporated, and the residue was dissolved in H_2O-CH_2Cl_2. The layers were separated and the aqueous phase was extracted with CH_2Cl_2. The organic extracts were dried and evaporated to yield an oil which was flash chromatographied (99:1, CH_2Cl_2-MeOH) to obtain **4** (219 mg, 66%) as an epimeric mixture on C-3: IR ($CHCl_3$) 3600-3400 (OH), 1731 cm^{-1} (CO); ^1H NMR 0.30* and 0.40 (2 t, *J*=7 Hz, 3H each, CH_3CH_2), 1.10-1.20 and 1.20-1.50 (m, CH_2CH_3), 1.75-1.90 (m, 5-H), 1.90-2.15 (m, 6-Ha), 2.30-2.45 (m, 6-He), 2.50-2.70 (m), 2.80 (d, *J*=12 Hz, CH_ACO_2Me), 2.95 (dd, *J*=12 and 2 Hz, CH_BCO_2Me), 3.00-3.20 (m, NCH_2), 3.20 and 3.50* (2 s, 3H each, OMe), 3.49-3.52 (m, CH_2OH), 3.80-4.05 (m, 2-H and OCH_2), 7.10-7.35 and 7.60-8.10 (2m, Ar-H); ^{13}C NMR 13.1 and 13.7 (CH_3CH_2), 20.3 and 22.2 (CH_3CH_2), 34.6 (C-5), 44.2 and 45.2 (CH_2CO_2Me), 48.9 and 49.3 (NCH_2), 50.5 and 51.0 (OMe), 55.3 and 55.5 (C-6), 58.2 (C-2), 63.6 and 63.8 (CH_2OH), 64.1 (OCH_2), 108.0 (C-4), 114.2 (In-C7), 120.7 and 121.1 (In-C5), 123.5 and 123.6 (In-C4), 125.4 and 125.5 (In-C6), 126.9 (C-*o*), 129.3 (C-*m*), 133.9 (C-*p*), 135.0 (C-*i*), 138.3 (In-C7a), 172.3 and 174.0 (CO_2Me); MS (*m/z*, %) 542 (M^+, 0.5), 511 (M^+-CH_2OH, 18), 497 (3), 401 (3), 215 (7), 187 (8), 128 (100). Anal. Calcd for $C_{28}H_{34}N_2O_7S.H_2O$: C, 59.98; H, 6.47; N, 4.99. Found: C, 59.86; H, 6.03; N, 4.96.

Methyl 2-Ethyl-*N*-triptophyl-4-oxopiperidine-3-acrylates (*Z*- and *E*-19). To a solution of aminoalcohols **4** (155 mg, 0.28 mmol) in dry THF (25 ml), cooled at 0°C and under Ar atmosphere, freshly sublimed K^{t}BuO (96 mg, 0.85 mmol) was added. The solution was stirred at 0°C for 30 min

(tlc showed no more starting material). Freshly distilled $BF_3.Et_2O$ (50 µl, 0.56 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The crude mixture was poured on ice-water, basified with $NaHCO_3$ and extracted first with Et_2O and then with CH_2Cl_2. The organic extracts were dried and evaporated thus obtaining an oil which was flash chromatographied (SiO_2, 90:10, CH_2Cl_2-MeOH) to give *Z*-and *E*-**19**. Acrylate *E*-**19** (Higher Rf, 35 mg, 36%): IR (NaCl) 1728 (CO), 1588 cm^{-1} (C=C); ^1H NMR 0.90 (t, *J*= 7 Hz, 3H, CH_3CH_2), 1.10-1.25 (m, 1H, CH_ACH_3), 1.40-1.60 (m, 1H, CH_BCH_3), 2.39 (t, *J*=7 Hz, 2H, β-H), 2.99 (t, *J*=7 Hz, 2H, 5-H), 3.36 (t, *J*=7 Hz, 2H, α-H), 3.43 (t, *J*= 7 Hz, 1H, 2-H), 3.50 (t, *J*=7 Hz, 2H, 6-H), 3.52 (s, 3H, OMe), 6.87 (s, 1H, HC=), 6.94 (d, *J*=2 Hz, 1H, In-2H), 7.06 (t, *J*=7 Hz, 1H, In-5H), 7.14 (t, *J*=7 Hz, 1H, In-6H), 7.31 (d, *J*= 7 Hz, 1H, In-7H), 7.48 (d, *J*= 7 Hz, 1H, In-4H), 8.28 (br s, 1H, In-NH); ^{13}C NMR 13.0 (CH_3CH_2), 26.5 (CH_3CH_2), 26.8 (C-5), 36.0 (Cβ), 43.0 (C-2), 48.0 (Cα), 52.5 (C-6), 58.0 (OMe), 113.0 (In-C7), 119.5 (In-C4), 121.0 (In-C5), 123.5 (In-C6), 124.0 (In-C2), 154.0 (HC=), 176.5 (COO), 188.8 (CO); MS (*m/z*, %) 340 (M^+, 35), 281 (36), 256 (33), 210 (100), 144 (84), 130 (75). Acrylate *Z*-**19** (Lower Rf, 30 mg, 31%): IR ($CHCl_3$) 3477 (NH), 1726 (CO), 1619 cm^{-1} (C=C); ^1H NMR 0.70 (t, *J*=7 Hz, 3H, CH_2CH_3), 1.20-1.40 (m, 1H, CH_ACH_3), 1.60-1.90 (m, 1H, CH_BCH_3), 2.45 (t, *J*=7 Hz, 2H, β-H), 2.75 (t, *J*=7 Hz, 2H, 5-H), 3.05 (t, *J*=7 Hz, 2H, α-H), 3.40 (t, *J*= 7 Hz, 1H, 2-H), 3.55 (t, *J*=7 Hz, 2H, 6-H), 3.70 (s, 3H, OMe), 6.50 (s, 1H, HC=), 6.95-7.50 (m, 5H, Ar-H), 8.55 (br s, 1H, In-NH); ^{13}C NMR 12.1 (CH_3CH_2), 22.8 (CH_3CH_2), 24.6 (C-5), 29.7 (Cβ), 34.3 (C-2), 46.7 (Cα), 48.9 (C-6), 56.8 (OMe), 111.5 (In-C7), 117.9 (In-C4), 119.6 (In-C5), 122.3 (In-C6), 128.3 (In-C2), 155.9 (HC=), 176.0 (CO_2Me); MS (*m/z*, %) 340 (M^+, 20), 327 (52), 282 (50), 196 (65), 151 (45), 144 (70), 130 (100). Anal. Calcd for $C_{20}H_{24}N_2O_3.3/2\ H_2O$: C, 65.38; H, 7.41; N, 7.62. Found: C, 65.47; H, 7.10; N, 7.26.

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