José L. Marco* and Gema Martín

Instituto de Química Orgánica General (CSIC), Juan de la Cierva, 3, 28006, Madrid, Spain

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The synthesis of some 2'-[2-(5-benzyloxyindolyl)]propylamine derivatives **1-15** from 2-(5-benzyloxyindole)carboxyaldehyde (**16**) and 2-(5-benzyloxy-1-methylindole) carboxyaldehyde (**17**) is reported. Compounds **1-15** have been designed as potential monoamine oxidase A and B inhibitors.

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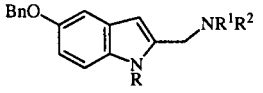
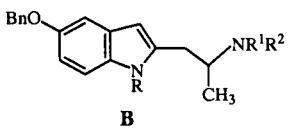
Introduction.

The mitochondrial enzyme monoamine oxidase is responsible for the deamination of biogenic amines, including those that function as neurotransmitters [1]. The importance of monoamine oxidase inhibitors as antidepressants has been recognized since the mood-elevating action of iproniazid was observed while testing this drug as a potential tuberculostatic agent. Johnston reported the existence of two monoamine oxidase forms [2], and defined monoamine oxidase-A as being sensitive to inhibition by clorgyline, whereas monoamine oxidase-B is sensitive to inhibition by l-deprenyl. Monoamine oxidase-A selective inhibitors are of interest as antidepressive agents while the monoamine oxidase-B selective inhibitor, l-deprenyl, is being used together with l-dopa in the treatment of Parkinson's disease [3]. The structural features that are responsible for a greater potency and selectivity towards either of the monoamine oxidases are still not completely clear, despite the large number of monoamine oxidase inhibitors that have been described [3].

In a recent study, Fernández-Alvarez and coworkers [4] described the synthesis and biological evaluation of a series of 2-(5-benzyloxyindolyl)methylamine derivatives **A** and found that these compounds were monamine oxidase-A inhibitors, but showed no selectivity. As a part of a project aimed at determining the structural features that should lead to an increased inhibitory potency and selectivity of this type of compounds, we have synthesized a series of new indole derivatives (**B**) that partially retain the functionalities present in compounds (**A**) but with an additional enlarged and α-branched alkyl chain at C-2 of the indole ring. We wanted to evaluate the effect of extending and branching the alkyl chain in the inibitory efficiency. In view of this, we report here the synthesis of compounds **1-15**.

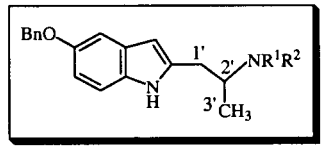


A

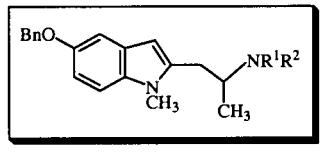


B

(R = H, CH_3; R^1, R^2 = H, CH_3, propargyl, 2-butynyl, 2,3-butadienyl)



1 R^1, R^2 = H
2 R^1 = H; R^2 = $CH_2C{\equiv}CH$
3a R^1 = H; R^2 = $CH_2C{\equiv}CCH_3$
3b R^1, R^2 = $CH_2C{\equiv}CCH_3$
4a R^1 = H; R^2 = $CH_2CH{=}C{=}CH_2$
4b R^1, R^2 = $CH_2CH{=}C{=}CH_2$
5 R^1 = H; R^2 = COOEt
6 R^1 = H; R^2 = CH_3
7 R^1 = CH_3; R^2 = $CH_2C{\equiv}CH$
8 R^1 = CH_3; R^2 = $CH_2C{\equiv}CCH_3$
9 R^1 = CH_3; R^2 = $CH_2CH{=}C{=}CH_2$



10 R^1, R^2 = H
11 R^1 = H; R^2 = $CH_2C{\equiv}CH$
12 R^1 = H; R^2 = $CH_2C{\equiv}CCH_3$
13 R^1 = H; R^2 = $CH_2CH{=}C{=}CH_2$
14 R^1 = H; R^2 = COOEt
15 R^1 = H; R^2 = CH_3

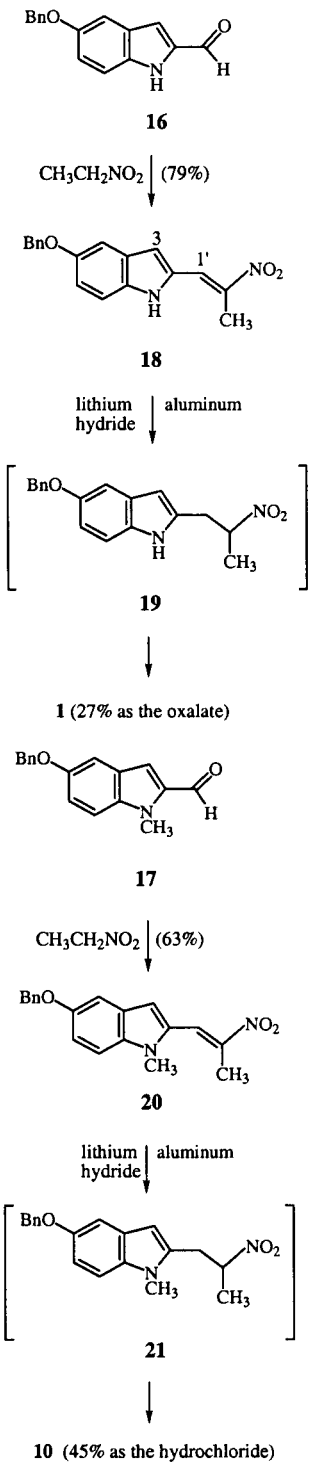
The biological evaluation and other biological parameters will be described elsewhere.

Results and Discussion.

The selected compounds have been prepared as shown in Scheme 1. Compounds **1-9** and **10-15** have been synthesized from 2-(5-benzyloxyindole)carboxyaldehyde (**16**)

and 2-(5-benzyloxy-1-methylindole)carboxyaldehyde (**17**), respectively. These aldehydes have been obtained from the corresponding ethyl carboxylates by reduction with lithium aluminium hydride and oxidation with manganese dioxide according to the published procedures [5, 6, 7].

Scheme 1



Our approach to the final desired molecules was based on the Henry reaction [8] of these aldehydes with nitroethane followed by reduction of the expected Knoevenagel products. To our knowledge, this sequence leading to the desired isotryptamines is novel and has not been covered before (see references 4, 5 and 7 for our previous work in this area).

This protocol was very efficient and afforded products **18** and **20** in good yield; only one isomer was detected and isolated; the configuration at the double bond was not established. In the ^{1}H nmr spectra we could observe the vinyl proton H-1' at δ = 8.07 and H3 at δ = 6.87, as a singlets. Reduction of these adducts with lithium aluminium hydride cleanly gave the primary amines **1** and **10** under mild conditions, in a "one-pot" reaction, *via* the nitro compounds **19** and **21**, that we did not try to isolate.

The formation of the secondary amines **2**, **3a**, **4a**, and **11-13** has been carried out by *N*-alkylation using the appropriate alkylating agent, under basic catalysis (*t*-butylamine) [4]. The yield was moderate (~30%) mainly due to the formation of minor amounts bis-alkylated products. In this series we could isolate and characterize only compounds **3b** and **4b**. In the case of the *N*-methylated indole products the formation of these secondary by-products was probably prevented by steric hindrance and were not detected.

The *N*-methyl secondary amines **6** and **15** have been prepared by the carbamate method. This is the best sequence in terms of efficiency and chemical yield. Thus, starting from the amines **1** and **10** the ethyl carbamates **5** and **14** were obtained and reduced with lithium aluminum hydride to the corresponding amines.

Finally, the *N*-methyl tertiary amines **7-9** were obtained from the parent amine **6** by *N*-alkylation, using the same protocol as described before.

All crude amines have been conveniently characterized by the formation of the corresponding hydrochlorides or acid oxalates, and gave excellent spectroscopic and analytical data. For instance, in the ^{1}H nmr spectra of compound **1** or **10** we could observe H-2' as a multiplet at δ = 3.52, coupled to protons H 1 and H-1' appearing at δ = 3.02 (dd, J = 14.6, 5.0 Hz) and at δ = 2.83 (dd, J = 14.6, 8.8 Hz), respectively; the CH_3-3' signal appears at δ = 1.17 as a doublet (J = 6.2 Hz). In the ^{1}H nmr spectra of compounds **2** or **11**, in addition to these significant signals, we analyzed also a doublet for $CH_2C{\equiv}CH$ at δ = 3.91 (J = 2.0 Hz) and a triplet for $CH_2C{\equiv}CH$ at δ = 3.61. In the ^{1}H nmr spectra of compounds (**3a**) or (**12**), we observed broad singlets at δ = 3.82 for $CH_2C{\equiv}CCH_3$ and at δ = 1.87 for $CH_2C{\equiv}CCH_3$. In the ^{1}H nmr spectra of compounds **4a** or **13**, we analyzed also signals at δ = 5.37

as a multiplet for N-CH_2CH=C=CH_2, at δ = 5.03 as a doublet (J = 6.7 Hz) for N-CH_2CH=C=CH_2 and at δ = 3.59 as a multiplet for N-CH_2CH=C=CH_2.

In summary, in this work we have reported and described, efficient and simple routes for the formation of 2'-[2-(5-benzyloxyindolyl)]propylamine derivatives starting from readily available materials. These amines are presumed neurotransmitters, designed to test the inhibition of monamine oxidase-A and B. This biological activity is being tested and will be reported in due course [9].

EXPERIMENTAL

Reactions were monitored by tlc using precoated silica gel alumina plates containing a fluorescent indicator (Merck, 5539). Detection was done by uv (254 nm) followed by charring with sulfuric-acetic acid spray, 1% aqueous potassium permanganate solution or 0.5% phosphomolybdic acid in 95% ethanol. Anhydrous sodium sulfate was used to dry organic solutions during workup and the removal of solvents was carried out under vacuum with a rotary evaporator. Flash column chromatography was performed using Kieselgel 60 (230-400 mesh, Merck) and hexane-ethyl acetate mixtures as eluent. ^{1}H spectra were recorded with a Varian VXR-300S spectrometer, using tetramethylsilane as internal standard.

General Method for the *N*-Alkylation of the Primary or Secondary Amines.

A solution of the respective amine (1 mmole) in dry tetrahydrofuran (50 ml) and *t*-butylamine (1.5 mmoles) was cooled at 0°. To this stirred mixture a solution of the appropriate acetylenic or allenic bromide (1.2 mmoles) was added dropwise. The mixture was stirred at room temperature until the reaction was complete (tlc analysis). The solvent was removed in vacuum, the residue treated with water and extracted with ethyl ether. Flash chromatography was used for product isolation.

2-(5-Benzyloxyindole)carboxyaldehyde (**16**).

Ethyl 2-(5-benzyloxyindole)carboxylate [5] (10 g, 0.035 mole) was suspended in dry tetrahydrofuran (200 ml) and treated with lithium aluminium hydride (8 g, 0.21 mole, 6 equivalents) at reflux for 4 hours; after 2 hours at room temperature, the flask was cooled at 0° and the excess of lithium aluminum hydride destroyed by careful addition of water. The solid was removed by filtration and washed with tetrahydrofuran several times. The solvent was evaporated and the residue dissolved in ethyl ether, dried and evaporated to give the alcohol (**5**) as a yellow solid (recrystallized from benzene, mp 106°; 7 g, 93% yield), that without further analysis was submitted to oxidation as follows: The alcohol (3 g, 0.011 mole), dissolved in dry tetrahydrofuran (150 ml), was treated with manganese dioxide (12.5 g, 0.14 mole, 12.7 equivalents) and sodium chloride (2.5 g); the suspension was stirred rapidly for 90 hours at room temperature. After this period a saturated aqueous solution of sodium chloride (25 ml) was added and the mixture stirred for 2 hours. After filtration over Celite, the solvent was removed to give a solid that was recrystallized from benzene to give pure aldehyde **16** (2.35 g, 93% yield), mp 180-181°; ir (potassium bromide): ν 3320 (NH), 1650 (CO) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 9.80 (s, 1 H, CHO), 9.17 (br s, 1 H, NH), 7.50-7.15 (m, 9 H, aromatic H), 5.10 (s, 2 H, OCH_2).

Anal. Calcd. for $C_{16}H_{13}NO_2$ (251.2): C, 76.49; H, 5.17; N, 5.57. Found: C, 76.25; H, 5.40; N, 5.65.

Adduct **18**.

A mixture of the aldehyde **16** (1.2 g mg, 5 mmoles), ammonium acetate (440 mg, 5.2 mmoles) and nitroethane (580 mg, 8 mmoles) dissolved in ethanol (15 ml) was refluxed for 1 hour, then 16 hours at room temperature and again at reflux for 6 hours. The solvent was removed and the residue diluted with ethyl acetate, washed with water, dried and evaporated. The residue was recrystallized from benzene-methanol to give compound **18** (1.1 g, 79%), mp 160-162°; ir (potassium bromide): ν 3600-3100 (NH) cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 8.30 (br s, 1 H, NH), 8.07 [s, 1 H, $CHC(NO_2)CH_3$], 7.49-7.26 (m, 6 H, aromatic H), 7.13 (d, J = 2.3 Hz, 1 H, H-4), 7.06 (dd, J = 8.9, 2.3 Hz, 1 H, H-6), 6.87 (s, 1 H, H-3), 5.11 (s, 2 H, OCH_2), 2.60 [s, 3 H, $CHC(NO_2)CH_3$].

Anal. Calcd. for $C_{18}H_{16}N_2O_3$ (308.3): C, 70.12; H, 5.19; N, 9.09. Found: C, 70.07; H, 5.16; N, 9.20.

2'-[2-(5-Benzyloxyindolyl)]propylamine (**1**).

A solution of compound **18** (800 mg, 2.5 mmoles) in dry tetrahydrofuran (10 ml) was added dropwise to a suspension of lithium aluminum hydride (1 g, 26 mmoles) in dry tetrahydrofuran (30 ml). The reaction was refluxed for 2 hours and stirred at room temperature for 24 hours. The excess of lithium aluminum hydride was destroyed with water, the reaction was filtered and the solid washed with tetrahydrofuran. The solvent was removed and the residue was dissolved in ethyl ether, dried and the crude amine **1** was transformed into the oxalate acid (250 mg, 27% overall yield after recrystallization), mp 118-119°; ir (potassium bromide): ν 3600-2500 (NH, NH_3) cm^{-1}; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 11.03 (br s, 1 H, NH), 7.49-7.30 (m, 5 H, aromatic H), 7.22 (d, J = 8.7 Hz, 1 H, H-7), 7.05 (d, J = 2.2 Hz, 1 H, H-4), 6.76 (dd, J = 8.7, 2.3 Hz, 1 H, H-6), 6.18 (s, 1 H, H-3), 5.24-5.04 (br s, 3 H, NH_3^+), 5.09 (s, 2 H, OCH_2), 3.52 [m, 1 H, $CH_2CH(NH_3)CH_3$], 3.02 [dd, J = 14.6, 5.0 Hz, 1 H, $CH_2CH(NH_3)CH_3$], 2.83 [dd, J = 14.6, 8.8 Hz, 2 H, $CH_2CH(NH_3)CH_3$], 1.17 [d, J = 6.2 Hz, 3 H, $CH_2CH(NH_3)CH_3$].

Anal.. Calcd. for $C_{20}H_{22}N_2O_5$ (370.4): C, 64.86; H, 5.94; N, 7.56. Found: C, 64.58; H, 5.95; N, 7.33.

N-(2-Propynyl)-2'-[2-(5-benzyloxyindolyl)]propylamine **2**.

Following the General method amine **1** (1.4 g, 5 mmoles) was transformed into amine **2** (520 mg, 32%) isolated after flash chromatography eluting with chloroform:methanol (15:1).

Compound **2** oxalate had mp 142-144°; ir (potassium bromide): ν 3600-3100 (NH, NH_2^+) cm^{-1}; ^{1}H nmr (deuterated dimethyl sulfoxide): δ 10.97 (br s, 1 H, NH), 7.47-7.28 (m, 5 H, aromatic H), 7.22 (d, J = 8.4 Hz, 1 H, H-7), 7.04 (d, J = 2.5 Hz, 1 H, H-4), 6.76 (dd, J = 8.8, 2.5 Hz, 1 H, H-6), 6.19 (s, 1 H, H-3), 6.24-5.84 (br s, 2 H, NH_2^+), 5.08 (s, 2 H, OCH_2), 3.91 (d, J = 2.0 Hz, 2 H, $CH_2C{\equiv}CH$), 3.61 (t, J = 2.0 Hz, 1 H, $CH_2C{\equiv}CH$), 3.58 [m, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CH)CH_3$], 3.18 [dd, J = 14.6, 4.4 Hz, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CH)CH_3$], 2.80 [dd, J = 14.6, 9.3 Hz, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CH)CH_3$], 1.17 [d, J = 6.3 Hz, 3 H, $CH_2CH(NH_2CH_2C{\equiv}CH)CH_3$].

Anal. Calcd. for $C_{23}H_{24}N_2O_5$ (408.4): C, 67.81; H, 5.65; N, 6.87. Found: C, 67.58; H, 5.38; N, 6.95.

N-(2-Butynyl)-2'-[2-(5-benzyloxyindolyl)]propylamine (**3a**) and *N,N'*-Bis-(2-butynyl)-2'-[2-(5-benzyloxyindolyl)]propylamine (**3b**).

Following the General method amine **1** (2 g, 5.4 mmoles) was transformed into *N*-propargylamine (**3a**) (500 mg, 27%) and *N,N'*-bis-propargylamine (**3b**) (32 mg, 1%) isolated after flash chromatography eluting with acetonitrile.

The **3a** oxalate had mp 125°; ir (potassium bromide): ν 3600-3100 (NH, NH_2^+) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 11.0 (br s, 1 H, NH), 7.48-7.27 (m, 5 H, aromatic H), 7.21 (d, J = 8.7 Hz, 1 H, H-7), 7.03 (d, J = 2.4 Hz, 1 H, H-4), 6.75 (dd, J = 8.7, 2.4 Hz, 1 H, H-6), 6.25 (s, 1 H, H-3), 6.24-5.84 (br s, 2 H, NH_2^+), 5.07 (s, 2 H, OCH_2), 3.82 (s, 2 H, $CH_2C{\equiv}CCH_3$), 3.53 [m, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CCH_3)CH_3$], 3.17 [dd, J = 14.3, 4.4 Hz, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CCH_3)CH_3$], 2.80 [dd, J = 14.3, 9.1 Hz, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CCH_3)CH_3$], 1.87 (s, 3 H, $CH_2C{\equiv}CCH_3$), 1.14 [d, J = 6.4 Hz, 3 H, $CH_2CH(NH_2CH_2C{\equiv}CCH_3)CH_3$].

Anal. Calcd. for $C_{24}H_{26}N_2O_5$ (422.4): C, 68.24; H, 6.16; N, 6.63. Found: C, 68.22; H, 6.25; N, 6.74.

Compound **3b** hydrochloride had mp 138-140°; ^1H nmr (deuterated dimethyl sulfoxide): δ 11.08 (br s, 1 H, NH), 7.47-7.28 (m, 5 H, aromatic H), 7.22 (d, J = 8.4 Hz, 1 H, H-7), 7.04 (d, J = 2.4 Hz, 1 H, H-4), 6.76 (dd, J = 8.8, 2.4 Hz, 1 H, H-6), 6.17 (s, 1 H, H-3), 5.07 (s, 2 H, OCH_2), 4.14 (br s, 4 H, 2 x $CH_2C{\equiv}CCH_3$), 3.53 {m, 1 H, $CH_2CH[NH(CH_2C{\equiv}CCH_3)_2]CH_3$}, 3.17 {dd, J = 14.3, 4.4 Hz, 1 H, $CH_2CH[NH(CH_2C{\equiv}CCH_3)_2]CH_3$}, 2.80 {dd, J = 14.3, 9.1 Hz, 1 H, $CH_2CH[NH(CH_2C{\equiv}CCH_3)_2]CH_3$}, 1.92 (s, 6 H, 2 x $CH_2C{\equiv}CCH_3$), 1.26 (d, J = 6.4 Hz, 3 H, $CH_2CH[NH(CH_2C{\equiv}CCH_3)_2]CH_3$}.

Anal. Calcd.for $C_{26}H_{29}ClN_2O$ (420.9): C, 74.19; H, 6.89; N, 6.65; Cl, 8.44. Found: C, 74.22; H, 7.16; N, 6.65; Cl, 8.12.

N-(2,3-Butadienyl)-2'-[2-(5-benzyloxyindolyl)]propylamine (**4a**) and *N,N'*-Bis-(2-butynyl)-2'-[2-(5-benzyloxyindolyl)]propylamine (**4b**).

Following the General method amine **1** (1.85 g, 5.0 mmoles) was transformed into *N*-propargylamine (**4a**) (320 mg, 20%) and *N,N'*-bis-propargylamine (**4b**) (52 mg, 3%), isolated after flash chromatography eluting with chloroform:methanol (10:1).

Compound **4a** oxalate had mp 108-109°; ir (potassium bromide): ν 3600-3100 (NH, NH_2^+) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 10.95 (br s, 1 H, NH), 7.47-7.26 (m, 5 H, aromatic H), 7.21 (d, J = 8.7 Hz, 1 H, H-7), 7.03 (d, J = 2.4 Hz, 1 H, H-4), 6.74 (dd, J = 8.7, 2.4 Hz, 1 H, H-6), 6.16 (s, 1 H, H-3), 6.84-6.54 (br s, 2 H, NH_2^+), 5.37 (m, 1 H, $CH_2CH{=}C{=}CH_2$), 5.06 (s, 2 H, OCH_2), 5.03 (d, J = 6.7 Hz, 2 H, $CH_2CH{=}C{=}CH_2$), 3.59 (m, 2 H, $CH_2CH{=}C{=}CH_2$), 3.53 [m, 1 H, $CH_2CH(NH_2CH_2CH{=}C{=}CH_2)CH_3$], 3.20 [dd, J = 14.5, 4.4 Hz, 1 H, $CH_2CH(NH_2CH_2CH{=}C{=}CH_2)CH_3$], 2.90 [dd, J = 14.5, 9.3 Hz, 1 H, $CH_2CH(NH_2CH_2CH{=}C{=}CH_2)CH_3$], 1.17 [d, J = 6.4 Hz, 3 H, $CH_2CH(NH_2CH_2CH{=}C{=}CH_2)CH_3$].

Anal. Calcd. for $C_{24}H_{26}N_2O_5$ (422.4): C, 68.24; H, 6.16; N, 6.63. Found: C, 68.26; H, 6.40; N, 6.88.

Compound **4b** oxalate had mp 100-102°; ir (potassium bromide): ν 3600-3100, 3250 (NH, NH^+) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 10.85 (br s, 1 H, NH), 7.50-7.30 (m, 5 H, aromatic H), 7.23 (d, J = 8.8 Hz, 1 H, H-7), 7.04 (d, J = 2.2 Hz, 1 H, H-4), 6.77 (dd, J = 8.8, 2.2 Hz, 1 H, H-6), 6.17 (s, 1 H, H-3), 6.84-6.54 (br s, 1 H, NH^+), 5.35 (m, 2 H, 2 x $CH_2CH{=}C{=}CH_2$), 5.07 (s, 2 H, OCH_2), 5.05 (m, 4 H, 2 x $CH_2CH{=}C{=}CH_2$), 3.73 (m, 4 H, 2 x $CH_2CH{=}C{=}CH_2$), 3.68 {m, 1 H, $CH_2CH[NH(CH_2CH{=}C{=}CH_2)_2]CH_3$}, 3.20 {dd, J = 14.5, 4.4 Hz, 1 H, $CH_2CH[NH(CH_2CH{=}C{=}CH_2)_2]CH_3$}, 2.90 {dd, J = 14.5, 9.3 Hz, 1 H, $CH_2CH[NH(CH_2CH{=}C{=}CH_2)_2]CH_3$}, 1.16 {d, J = 6.6 Hz, 3 H, $CH_2CH[NH(CH_2CH{=}C{=}CH_2)_2]CH_3$}.

Anal. Calcd. for $C_{28}H_{30}N_2O_5$ (474.5): C, 70.88; H, 6.32; N, 5.90. Found: C, 70.59; H, 6.39; N, 5.85.

N-(Methyl)-2'-[2-(5-benzyloxyindolyl)]propylamine (**6**).

To a cooled mixture at 0° of the **1** oxalate (3.2 mmoles) in an aqueous solution of sodium hydroxide (10 ml, 20 mmoles, 2*N*) and benzene (10 ml), ethyl chloroformate (434 mg, 4 mmoles) dissolved in benzene (3 ml) was added dropwise. After the addition, the reaction was stirred at room temperature for 2 hours. The organic phase was separated and the aqueous layer was extracted several times with benzene. The organic phase was finally dried, filtered and evaporated. The resulting ethyl carbamate **5** was pure enough for the next step (1 g, 91% yield); carbonate **5** had ^1H nmr (deuterated dimethyl sulfoxide): δ 8.20 (br s, 1 H, NH), 7.49-7.25 (m, 5 H, aromatic H), 7.18 (d, J = 8.7 Hz, 1 H, H-7), 7.07 (d, J = 2.5 Hz, 1 H, H-4), 6.88 (dd, J = 8.7, 2.5 Hz, 1 H, H-6), 6.18 (s, 1 H, H-3), 5.09 (s, 2 H, OCH_2), 4.12 (t, J = 7.1 Hz, 2 H, $COOCH_2CH_3$), 4.04 [m, 1 H, $CH_2CH(NHCOOCH_2CH_3)CH_3$], 2.90 [m, 2 H, $CH_2CH(NHCOOCH_2CH_3)CH_3$], 1.20 (q, J = 7.1 Hz, 3 H, $COOCH_2CH_3$), 1.18 [d, J = 6.6 Hz, 3 H, $CH_2CH(NHCOOCH_2CH_3)CH_3$].

This material was dissolved in dry tetrahydrofuran (35 ml) and treated with lithium aluminum hydride (1 g, 24 mmoles). This mixture was stirred 4 hours at room temperature, at reflux for 3 hours and at room temperature overnight. The lithium aluminum hydride in excess was destroyed with water, the mixture filtered and the solid washed with more tetrahydrofuran. The organic solvent was dried and evaporated. The resulting amine was transformed into the **6** oxalate (650 mg, 57% yield), mp 110-112°; ir (potassium bromide): ν 3600-3100, 3250 (NH, $NH_2CH_3^+$) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 11.0 (br s, 1 H, NH), 7.48-7.29 (m, 5 H, aromatic H), 7.22 (d, J = 8.6 Hz, 1 H, H-7), 7.04 (d, J = 2.4 Hz, 1 H, H-4), 6.77 (dd, J = 8.6, 2.4 Hz, 1 H, H-6), 6.18 (d, J = 1.0 Hz, 1 H, H-3), 6.84-6.54 (br s, 2 H, NH_2^+), 5.07 (s, 2 H, OCH_2), 3.50 [m, 1 H, $CH_2CH(NH_2CH_3)CH_3$], 3.20 [dd, J = 14.4, 4.7 Hz, 1 H, $CH_2CH(NH_2CH_3)CH_3$], 2.80 [dd, J = 14.4, 9.1 Hz, 1 H, $CH_2CH(NH_2CH_3)CH_3$], 2.58 (s, 3 H, NH_2CH_3), 1.18 [d, J = 6.5 Hz, 3 H, $CH_2CH(NH_2CH_3)CH_3$].

Anal. Calcd. for $C_{21}H_{24}N_2O_5$ (384.4): C, 65.62; H, 6.25; N, 7.29. Found: C, 65.50; H, 6.26; N, 7.54.

N-(2-Propynyl)-*N'*-(methyl)-2'-[2-(5-benzyloxyindolyl)]propylamine (**7**).

Following the General method amine **6** oxalate (1.0 g, 2.6 mmoles) was transformed into (**7**) (570 mg, 65%), isolated after flash chromatography eluting with chloroform:methanol (20:1).

Compound **7** hydrochloride had mp 153-155°; ir (potassium bromide): ν 3600-3100, 3280 (NH, $NHCH_3^+$) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 11.30 (br s, 1 H, NH), 11.10 (br s, 1 H, $NHCH_3^+$), 7.49-7.28 (m, 5 H, aromatic H), 7.23 (d, J = 8.7 Hz, 1 H, H-7), 7.04 (d, J = 2.3 Hz, 1 H, H-4), 6.76 (dd, J = 8.7, 2.3 Hz, 1 H, H-6), 6.20 (s, 1 H, H-3), 5.09 (s, 2 H, OCH_2), 4.20 (m, 2 H, $CH_2C{\equiv}CH$), 3.80 (br s, 1 H, $CH_2C{\equiv}CH$),

3.37 (m, 1 H, $CH_2CH(NHCH_3CH_2C{\equiv}CH)CH_3$], 2.90 (m, 5 H, $CH_2CH(NHCH_3CH_2C{\equiv}CH)CH_3$], 1.23 [d, J = 6.4 Hz, 3 H, $CH_2CH(NHCH_3CH_2C{\equiv}CH)CH_3$].

Anal. Calcd. for $C_{22}H_{25}ClN_2O$ (368.9): C, 71.64; H, 6.78; N, 7.59; Cl, 9.63. Found: C, 71.34; H, 6.74; N, 7.48; Cl, 9.20.

N-(2-Butynyl)-*N*'-(methyl)-2'-[2-(5-benzyloxyindolyl)]propylamine (**8**).

Following the General method amine **6** oxalate (1.0 g, 2.6 mmoles) was transformed into **8** (590 mg, 65%), isolated after flash chromatography eluting with acetonitrile.

Compound **8** hydrochloride had mp 128-130°; ir (potassium bromide): ν 3600-3100, 3280 (NH, $NHCH_3^+$) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 11.10 (br s, 1 H, NH), 10.90 (br s, 1 H, $NHCH_3^+$), 7.46-7.25 (m, 5 H, aromatic H), 7.23 (d, J = 8.7 Hz, 1 H, H-7), 7.03 (d, J = 2.2 Hz, 1 H, H-4), 6.75 (dd, J = 8.7, 2.2 Hz, 1 H, H-6), 6.16 (s, 1 H, H-3), 5.06 (s, 2 H, OCH_2), 4.08 (s, 2 H, $CH_2C{\equiv}CCH_3$), 3.32 (m, 1 H, $CH_2CH(NHCH_3CH_2C{\equiv}CCH_3)CH_3$], 2.85 [m, 5 H, $CH_2CH(NHCH_3CH_2C{\equiv}CCH_3)CH_3$], 1.91 [s, 3 H, $CH_2CH(NHCH_3CH_2C{\equiv}CCH_3)CH_3$], 1.20 [d, J = 6.4 Hz, 3 H, $CH_2CH(NHCH_3CH_2C{\equiv}CCH_3)CH_3$].

Anal. Calcd. for $C_{23}H_{27}ClN_2O$ (382.9): C, 72.15; H, 7.05; N, 7.32; Cl, 9.28. Found: C, 72.30; H, 7.31; N, 7.49; Cl, 9.34.

N-(2,3-Butadienyl)-*N*'-(methyl)-2'-[2-(5-benzyloxyindolyl)]-propylamine (**9**).

Following the General method amine **6** oxalate (1.0 g, 2.6 mmoles) was transformed into **9**, isolated after flash chromatography eluting with chloroform:methanol (15:1) and characterized as the **9** hydrochloride (320 mg, 34% yield), mp 136-138°; ir (potassium bromide): ν 3600-3100, 3280 (NH, $NHCH_3^+$) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 11.10 (br s, 1 H, NH), 10.90 (br s, 1 H, $NHCH_3^+$), 7.49-7.28 (m, 5 H, aromatic H), 7.23 (d, J = 8.7 Hz, 1 H, H-7), 7.06 (d, J = 2.2 Hz, H-4), 6.77 (dd, J = 8.7, 2.2 Hz, 1 H, H-6), 6.23 (s, 1 H, H-3), 5.60 (m, 1 H, $CH{=}C{=}CH_2$), 5.12 (d, J = 7.0 Hz, 2 H, $CH{=}C{=}CH_2$), 5.09 (s, 2 H, OCH_2), 3.80-2.90 [m, 5 H, $CH_2CH(NHCH_3CH_2CH{=}C{=}CH_2)CH_3$], 2.74 [s, 3 H, $CH_2CH(NHCH_3CH_2CH{=}C{=}CH_2)CH_3$], 1.22 [d, J = 6.4 Hz, 3 H, $CH_2CH(NHCH_3CH_2CH{=}C{=}CH_2)CH_3$].

Anal. Calcd. for $C_{23}H_{27}ClN_2O$ (382.9): C, 72.15; H, 7.05; N, 7.32; Cl, 9.28. Found: C, 71.89; H, 6.95; N, 7.04; Cl, 9.50.

2-(5-Benzyloxy-1-methylindole)carboxyaldehyde (**17**).

To a solution of ethyl 2-(5-benzyloxy-1-methylindole)carboxylate [6] (3 g, 10 mmoles) in dry tetrahydrofuran (60 ml), cooled in an ice bath, lithium aluminum hydride (1.89 g, 50 mmoles) was added. After the addition was complete, the reaction was stirred at room temperature for 2 hours. The flask was cooled and water was added dropwise to destroy the lithium aluminum hydride in excess. The solid was filtered, washed with tetrahydrofuran and the solvent removed. The crude 2-(5-benzyloxy-1-methylindole)methanol (2.67 g, 99% yield) was pure enough for the next step. For complete characterization purposes, a simple flash chromatography (hexane, ethyl acetate: 7/3) gave an analytical sample: [mp 100-102°; ir (potassium bromide): ν 3600-3100 (NH, OH) cm^{-1}; ^1H nmr (deuteriochloroform): δ 7.50-6.97 (m, 8 H, aromatic H), 6.35 (s, 1 H, H-3), 5.11 (s, 2 H, OCH_2), 4.72 (s, 2 H, CH_2OH), 3.72 (s, 3 H, NCH_3).

Anal. Calcd. for $C_{17}H_{17}NO_2$ (267.3): C, 76.38; H, 6.40; N, 5.23. Found: C, 76.44; H, 6.32; N, 5.11.

To a solution of this alcohol (2.67 g, 10 mmoles) in dry tetrahydrofuran (60 ml) manganese dioxide (8.69 g, 100 mmoles) and sodium chloride (2.33 g, 40 mmoles) were added at room temperature. This suspension was stirred at room temperature for three days. The reaction was filtered, the solid washed with methylene chloride and the solvent evaporated. The resulting crude was purified by flash chromatography (hexane, ethyl acetate: 9/1) to give indole **17** (2.38 g, 90%), mp 136-138°; ir (potassium bromide): ν 1675 (CO) cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.85 (s, 1 H, CHO), 7.50-7.10 (m, 9 H, aromatic H), 5.11 (s, 2 H, OCH_2), 4.08 (s, 3 H, NCH_3).

Anal. Calcd. for $C_{17}H_{15}NO_2$ (265.3): C, 76.96; H, 5.69; N, 5.27. Found: C, 76.85; H, 5.54; N, 5.15.

Adduct **20**.

A mixture of the aldehyde **17** (530 mg, 2 mmoles), ammonium acetate (154 mg, 2 mmoles) and nitroethane (225 mg, 3 mmoles) dissolved in ethanol (15 ml) was refluxed for 1 hour, at room temperature for 16 hours and again at reflux for 6 hours. The solvent was removed and the residue diluted with ethyl acetate, washed with water, dried and evaporated. The residue was recrystallized from benzene-ethanol to give compound **20** (400 mg, 63%), mp 138-140°; ^1H nmr (deuteriochloform): δ 8.23 (s, 1 H, aromatic H), 7.50-7.30 (m, 6 H, aromatic H), 7.20-7.05 (m, 2 H, aromatic H), 6.83 [s, 1 H, $CH{=}C(NO_2)CH_3$], 5.12 (s, 2 H, OCH_2), 3.82 (s, 3 H, NCH_3), 2.60 [s, 3 H, $CH{=}C(NO_2)CH_3$].

Anal. Calcd. for $C_{19}H_{18}N_2O_3$ (322.3): C, 70.80; H, 5.59; N, 8.69. Found: C, 71.13; H, 5.31; N, 8.56.

2'-[2-(5-Benzyloxy-1-methylindolyl)]propylamine (**10**).

A solution of compound **20** (880 mg, 2.7 mmoles) in dry tetrahydrofuran (10 ml) was added dropwise to a suspension of lithium aluminum hydride (1 g, 26 mmoles) in dry tetrahydrofuran (30 ml). The reaction was refluxed for 5 hours and stirred at room temperature for 18 hours. The excess of lithium aluminum hydride was destroyed with water; the reaction was filtered and the solid washed with tetrahydrofuran. The solvent was removed and the residue was dissolved in ethyl ether, dried and the crude amine **10** transformed into the hydrochloride (400 mg, 45% overall yield after recrystallization).

Compound **10** hydrochloride mp 178-180°; ir (potassium bromide): ν 3600-3300 (NH_3^+) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 8.25 (br s, 3 H, NH_3^+), 7.48-7.28 (m, 6 H, aromatic H), 7.06 (d, J = 2.4 Hz, 1 H, H-4), 6.83 (dd, J = 8.8, 2.4 Hz, 1 H, H-6), 6.24 (s, 1 H, H-3), 5.08 (s, 2 H, OCH_2), 3.64 (s, 3 H, NCH_3), 3.45 [m, 1 H, $CH_2CH(NH_3)CH_3$], 3.18 [dd, J = 14.8, 5.6 Hz, 1 H, $CH_2CH(NH_3)CH_3$], 2.95 [dd, J = 14.8, 8.6 Hz, 1 H, $CH_2CH(NH_3)CH_3$], 1.22 [d, J = 6.4 Hz, 3 H, $CH_2CH(NH_3)CH_3$].

Anal. Calcd. for $C_{19}H_{23}ClN_2O$ (330.8): C, 68.78; H, 6.95; N, 8.47; Cl, 10.74. Found: C, 68.84; H, 6.80; N, 8.40; Cl, 10.55.

N-(2-Propynyl)-2'-[2-(5-benzyloxy-1-methylindolyl)]propylamine (**11**).

Following the General method amine **10** hydrochloride (500 mg, 1.6 mmoles) was transformed into amine **11** (100 mg, 20%) isolated after flash chromatography eluting with ethyl acetate and characterized as the oxalate acid.

Compound **11** oxalate had mp 125-126°; ir (potassium bromide): ν 3600-3100, 3290 (NH_2^+) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 7.48-7.31 (m, 6 H, aromatic H), 7.08 (d, J = 2.3 Hz, 1 H, H-4), 6.84 (dd, J = 8.8, 2.3 Hz, 1 H, H-6), 6.24 (s, 1 H, H-3), 5.10 (s, 2 H, OCH_2), 3.94 (s, 2 H, $CH_2C{\equiv}CH$),

3.67 (s, 3 H, NCH_3), 3.65 (s, 1 H, $CH_2C{\equiv}CH$), 3.52 [m, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CH)CH_3$], 3.24 [dd, J = 14.6, 4.4 Hz, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CH)CH_3$], 2.90 [dd, J = 14.6, 9.7 Hz, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CH)CH_3$], 1.20 [d, J = 6.5 Hz, 3 H, $CH_2CH(NH_2CH_2C{\equiv}CH)CH_3$].

Anal. Calcd. for $C_{24}H_{26}N_2O_5$ (422.4): C, 68.24; H, 6.16; N, 6.63. Found: C, 68.04; H, 5.96; N, 6.49.

N-(2-Butynyl)-2'-[2-(5-benzyloxy-1-methylindolyl)]propylamine (**12**).

Following the General method amine **10** hydrochloride (1 g, 3.0 mmoles) was transformed into (**12**) isolated after flash chromatography eluting with acetonitrile and characterized as the oxalate acid (320 mg, 25%).

Compound **12** oxalate had mp 122-124°; ir (potassium bromide): ν 3600-3200 (NH_2^+) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 7.49-7.17 (m, 6 H, aromatic H), 7.09 (d, J = 2.3 Hz, 1 H, H-4), 6.85 (dd, J = 9.8, 2.3 Hz, 1 H, H-6), 6.24 (s, 1 H, H-3), 5.10 (s, 2 H, OCH_2), 3.90 (s, 2 H, $CH_2C{\equiv}CCH_3$), 3.68 (s, 3 H, NCH_3), 3.55 [m, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CCH_3)CH_3$], 3.28 [dd, J = 14.5, 4.0 Hz, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CCH_3)CH_3$], 2.90 [dd, J = 14.5, 8.8 Hz, 1 H, $CH_2CH(NH_2CH_2C{\equiv}CCH_3)CH_3$], 1.89 [s, 3 H, $CH_2CH(NH_2CH_2C{\equiv}CCH_3)CH_3$], 1.21 [d, J = 6.2 Hz, 3 H, $CH_2CH(NH_2CH_2C{\equiv}CCH_3)CH_3$].

Anal. Calcd. for $C_{25}H_{28}N_2O_5$ (436.5): C, 68.80; H, 6.42; N, 6.43. Found: C, 68.55; H, 6.21; N, 6.18.

N-(2,3-Butadienyl)-2'-[2-(5-benzyloxy-1-methylindolyl)]propylamine (**13**).

Following the General method amine **10** oxalate (1 g, 3.0 mmoles) was transformed into **13** isolated after flash chromatography eluting with chloroform:methanol (20:1) and characterized as the oxalate acid (330 mg, 25%).

Compound **13** oxalate had mp 141-142°; ir (potassium bromide): ν 3600-3150 (NH_2^+) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 7.45-7.28 (m, 6 H, aromatic H), 7.05 (d, J = 2.3 Hz, 1 H, H-4), 6.82 (dd, J = 9.8, 2.3 Hz, 1 H, H-6), 6.24 (s, 1 H, H-3), 5.33 (m, 1 H, $CH{=}C{=}CH_2$), 5.07 (s, 2 H, OCH_2), 5.04 (m, 2 H, $CH{=}C{=}CH_2$), 3.76 [m, 5 H, NCH_3, $CH_2CH(NH_2CH_2CH{=}C{=}CH_2)CH_3$], 3.55 [m, 1 H, $CH_2CH(NH_2CH_2CH{=}C{=}CH_2)CH_3$], 3.30 [dd, J = 14.6, 4.4 Hz, 1 H, $CH_2CH(NH_2CH_2CH{=}C{=}CH_2)CH_3$], 2.92 [dd, J = 14.6, 9.7 Hz, 1 H, $CH_2CH(NH_2CH_2CH{=}C{=}CH_2)CH_3$], 1.20 [d, J = 6.5 Hz, 3 H, $CH_2CH(NH_2CH_2CH{=}C{=}CH_2)CH_3$].

Anal. Calcd. for $C_{25}H_{27}N_2O_5$ (435.4): C, 69.21; H, 6.20; N, 6.43. Found: C, 69.40; H, 6.50; N, 6.49.

N-(Methyl)-2'-[2-(5-benzyloxy-1-methylindolyl)]propylamine (**15**).

To a cooled mixture of the **10** hydrochloride (720 mg, 2.1 mmoles) in an ice-bath, an aqueous solution of sodium hydroxide (10 ml, 20 mmoles, 2*N*) and benzene (13 ml), ethyl chloroformiate (270 mg, 2.5 mmoles) dissolved in benzene (3 ml) was added dropwise. After the addition, the reaction was stirred at room temperature for 3 hours. The organic phase was separated and the aqueous layer was extracted several times with benzene. The organic phase was finally dried, filtered and evaporated. The residue spontaneously crystallized to give ethyl carbamate **14** (720 mg, 94% yield), mp 78-79°; ^1H nmr (deuterated dimethyl sulfoxide): δ 7.50-7.26 (m, 5 H, aromatic H), 7.17 (d, J = 8.9 Hz, 1 H, H-7), 7.10 (d, J = 2.4 Hz, 1 H, H-4), 6.90 (dd, J = 8.9, 2.4 Hz, 1 H, H-6), 6.21 (s, 1 H, H-3), 5.10 (s, 2 H, OCH_2), 4.10 (t, J = 7.1 Hz, 2 H, $COOCH_2CH_3$), 3.97 [m, 1 H, $CH_2CH(NHCOOCH_2CH_3)CH_3$], 3.71 (s, 3 H, NCH_3), 3.00 [dd, J = 14.5, 5.3 Hz, 1 H, $CH_2CH(NHCOOCH_2CH_3)CH_3$], 2.73 [dd, J = 14.5, 7.9 Hz, 1 H, $CH_2CH(NHCOOCH_2CH_3)CH_3$], 1.23 (q, J = 7.1 Hz, 3 H, $COOCH_2CH_3$), 1.19 [d, J = 6.7 Hz, 3 H, $CH_2CH(NHCOOCH_2CH_3)CH_3$].

Anal. Calcd. for $C_{22}H_{26}N_2O_3$ (366.4): C, 72.13; H, 7.10; N, 7.65. Found: C, 72.40; H, 7.40; N, 7.84.

This material (700 mg, 20 mmoles) was dissolved in dry tetrahydrofuran (35 ml) and treated with lithium aluminum hydride (1 g, 24 mmoles). This mixture was stirred 1 hour at room temperature, at reflux for 4 hours and at room temperature overnight. The lithium aluminum hydride in excess was destroyed with water, the mixture filtered and the solid washed with more tetrahydrofuran. The organic solvent was dried and evaporated. The resulting amine was transformed into **15** oxalate (280 mg, 35% yield), mp 120-122°; ir (potassium bromide): ν 3600-3200, 3100 (NH_2^+) cm^{-1}; ^1H nmr (deuterated dimethyl sulfoxide): δ 7.48-7.29 (m, 6 H, aromatic H), 7.06 (d, J = 2.4 Hz, 1 H, H-4), 6.82 (dd, J = 8.6, 2.4 Hz, 1 H, H-6), 6.24 (s, 1 H, H-3), 6.24-5.54 (br s, 2 H, NH_2^+), 5.08 (s, 2 H, OCH_2), 3.66 (s, 3 H, NCH_3), 3.43 [m, 1 H, $CH_2CH(NH_2CH_3)CH_3$], 3.17 [dd, J = 14.4, 4.7 Hz, 1 H, $CH_2CH(NH_2CH_3)CH_3$], 2.88 [dd, J = 14.4, 9.1 Hz, 1 H, $CH_2CH(NH_2CH_3)CH_3$], 2.59 (s, 3 H, NH_2CH_3), 1.19 [d, J = 6.4 Hz, 3 H, $CH_2CH(NH_2CH_3)CH_3$].

Anal. Calcd. for $C_{22}H_{26}N_2O_5$ (398.4): C, 66.33; H, 6.53; N, 7.03. Found: C, 66.01; H, 6.79; N, 6.99.

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