Synthesis of 1-Alkyl-2,3-dihydro-2-(4-pyridinyl)-1*H*-isoindoles as Potential Selective Serotonin Reuptake Inhibitors

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Two 2,3-dihydro-2-(4-pyridinyl)-1*H*-isoindoles **2a,b** have been synthesized by the reaction of isoindoline with 4-chloropyridines. In addition, a number of 1-alkyl-2,3-dihydro-2-(4-pyridinyl)-1*H*-isoindoles **2c-h** were obtained from 2-(4-pyridinyl)phthalimide (**5**). The addition of alkyl Grignard reagents to **5** gave 1-alkylhydroxyisoindolones **6a-f** which, in two cases **6a,b**, were dehydrated and subjected to three separate reductions to give targets **2c,d**. In three cases, the intermediate hydroxyisoindolones **6c-e** were reduced in one step to the target compounds **2e-g** with lithium aluminum hydride-aluminum chloride. When **6f**, the product of the addition of phenyl Grignard to **5**, was subjected to these conditions, a hydroxyisoindoline **7** was obtained which was further reduced to **2h** with triethylsilane-trifluoroacetic acid. The lithium aluminum hydride-aluminum chloride conditions were successfully applied to the synthesis of a 1-benzyl-4-piperidine derivative **2i**.

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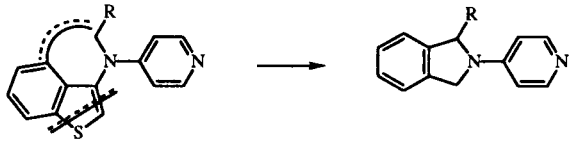
The selective serotonin reuptake inhibitors are compounds that are becoming increasingly important because of their potential use in a variety of neurological disorders [1]. We have recently reported a number of derivatives of 3-[(4-pyridinyl)amino]benzo[*b*]thiophene (**1**) [1], which are selective serotonin reuptake inhibitors (SSRIs) and, as such, may be useful in the treatment of Obsessive Compulsive Disorder (OCD) [2]. Among possible structural variations in this series, it occurred to us that 1-alkyl-2-pyridinylisoindolines **2** would contain most of the elements of **1** and possibly impart additional potency and selectivity.

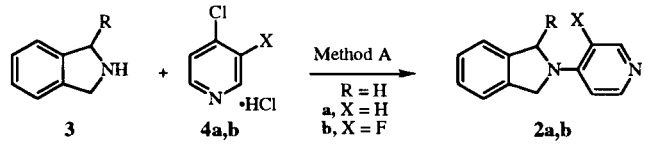


1 **2**

The initial approach to the title compounds was envisioned to proceed *via* the condensation of an appropriately substituted isoindoline with 4-chloropyridine hydrochloride as shown in Scheme 1. Although compounds **2a** and **2b** (Table 1) were prepared via this route, the synthesis of other derivatives (R ≠ H) was problematic in our hands. For example, 2,3-dihydro-1-methyl-1*H*-isoindole (**3**, R = CH_3) could be synthesized by the procedure of Rockell [3], but condensation with 4-chloropyridine gave a low yield. Furthermore, the synthesis of higher homologs of **3** (R = CH_2CH_3, $(CH_2)_2CH_3$), also gave low yields. As a result, a different route to these targets was investigated.

Alternatively, the target 3-methyl **2c** and 3-ethyl **2d** substituted isoindolines were prepared according to Scheme 2, method B. Treatment of 3-(4-pyridinyl)phthalimide (**5**) with an appropriate Grignard reagent [4] gave substituted

Scheme 1



3 **4a,b** **2a,b**

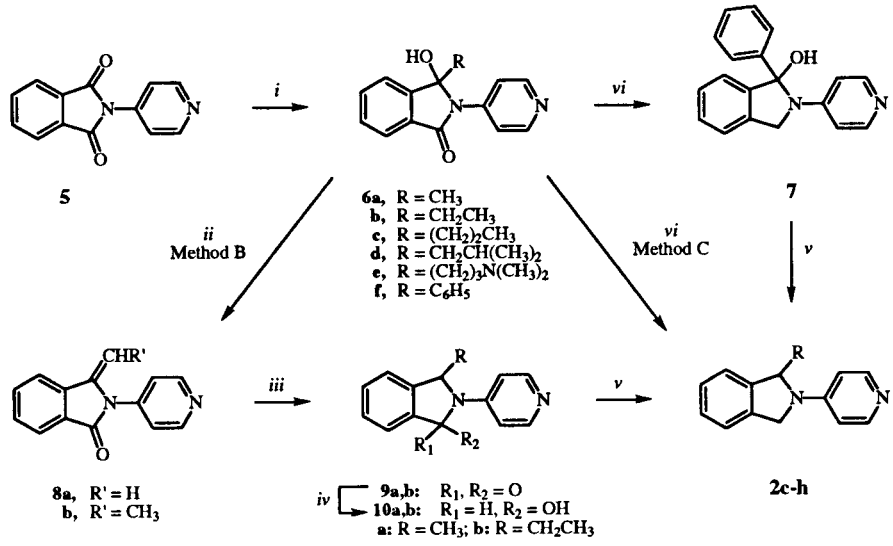
hydroxyisoindolones **6a,b** cleanly and in good yields. Alcohols **6a** and **6b** were then dehydrated by heating a mixture of compound and phosphorus pentoxide at 200° under vacuum, and the resulting double bond was then hydrogenated under standard conditions using palladium on carbon as catalyst. The resulting alkylisoindolones **9a,b** were then reduced to the stable hemiaminals **10a,b** using lithium aluminum hydride and these were further reduced to the desired isoindolines **2c,d** (Table 1) using triethylsilane/trifluoroacetic acid [5].

Further study of the reduction of the 3-substituted isoindolones **9** to the desired 3-substituted isoindolines **2** revealed that lithium aluminum hydride-aluminum chloride [6] would accomplish this transformation in one step. Furthermore, it was found that this reagent would reduce the 3-substituted-3-hydroxyisoindolones **6** directly to the 3-alkylsubstituted isoindolines **2** in most cases. Thus the synthesis of three target 3-substituted isoindolines **2e-g** (Table 1) was accomplished in two steps from the appropriately substituted phthalimide **5** (method C).

In the case of the 3-phenyl derivative **6f**, the aluminum hydride reduction gave only partial reduction to **7**. Further reduction to **2h** was accomplished with triethylsilane/trifluoroacetic acid.

The *N*-benzylpiperidine derivative **2i** (Table 1) was also prepared as described above for method C. Thus the starting 1-benzyl-4-phthalimidopiperidine [7] was treated with ethyl magnesium bromide and the resulting isoindolone was

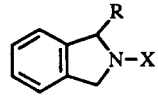
Scheme 2

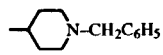


Reagents: (i) RMgBr, THF; (ii) P_2O_5, 200°, reduced pressure; (iii) Pd/C, H_2, THF; (iv) $LiAlH_4$, THF; (v) CF_3CO_2H, Et_3SiH, CH_2Cl_2; (vi) $LiAlH_4/AlCl_3$.

Table 1

1-Alkyl-2,3-dihydro-1*H*-isoindoles



Compound No.	Method/ Intermediate	X	R	Mp°C [a]	%Yield [b]	Molecular Formula	Analysis % Calcd./Found C	H	N
2a	A/4a		H	229 dec	11 [c]	$C_{13}H_{12}N_2 \cdot C_4H_4O_4$ [d]	65.38 65.30	5.16 5.07	8.97 8.91
2b	A/4b		H	204 dec	8 [c]	$C_{13}H_{11}FN_2 \cdot C_4H_4O_4$ [d]	61.82 61.86	4.58 4.39	8.48 8.43
2c	B/6a		CH_3	185 dec	19 [e]	$C_{14}H_{14}N_2 \cdot C_4H_4O_4$ [f]	66.25 65.99	5.56 5.49	8.58 8.42
2d	B/6b		CH_2CH_3	138 dec	62 [g]	$C_{15}H_{16}N_2 \cdot C_4H_4O_4$ [d]	67.05 66.84	5.92 5.95	8.23 8.18
2e	C/6c		$(CH_2)_2CH_3$	142 dec	34 [c]	$C_{16}H_{18}N_2 \cdot C_4H_4O_4$ [d]	67.78 67.63	6.26 6.08	7.90 7.76
2f	C/6d		$CH_2CH(CH_3)_2$	139 dec	45 [g]	$C_{17}H_{20}N_2 \cdot C_4H_4O_4$ [d]	68.46 68.18	6.57 6.63	7.60 7.53
2g	C/6e		$(CH_2)_3N(CH_3)_2$	221 dec	30 [g]	$C_{18}H_{23}N_3 \cdot 1.5C_4H_4O_4$ [h]	63.28 63.29	6.42 6.57	9.23 9.18
2h	C/6f		C_6H_5	164 dec	48 [g]	$C_{19}H_{16}N_2 \cdot C_4H_4O_4$ [d]	71.12 71.01	5.19 5.24	7.21 7.25
2i	C/[i]		CH_2CH_3	180 dec	42 [g]	$C_{22}H_{28}N_2 \cdot 2C_4H_4O_4$ [j]	65.20 65.00	6.57 6.73	5.07 5.00

[a] Melting points are uncorrected. [b] Yields are not optimized. [c] Crystallized from methanol. [d] Maleate salt. [e] Crystallized from ethanol/ethyl acetate. [f] Fumarate salt. [g] Crystallized from methanol/ethyl ether. [h] Sesquifumarate salt. [i] Not illustrated in Scheme 2. [j] Dimaleate salt.

reduced to the target **2i** using lithium aluminum hydride/aluminum chloride.

Although the 3-(4-pyridinyl)aminobenzo[*b*]thiophene derivatives **1** are potent and selective SSRIs [1], the 1-alkyl-2-pyridinylisoindolines **2** showed only weak activity.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Nicolet 205 FT-IR and nuclear magnetic resonance spectra were taken on a Gemini 200 instrument. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Mass spectral data were determined by direct insertion at 70 eV with a Finnigan 4500 GC-MS equipped with a INCOS data system. Flash chromatographic separations were performed using E. Merck 230-400 mesh silica gel as the solid phase. Elemental analyses were performed by Robertson Microlit Laboratories, Inc., Madison, NJ.

The preparation of 2,3-dihydro-1*H*-isoindole (**3**) has been described in the literature [8] as well as the preparation of 2-(4-pyridinyl)-1*H*-isoindole-1,3-(2*H*)-dione (**5**) [9].

Method A.

2,3-Dihydro-2-(4-pyridinyl)-1*H*-isoindole Maleate (**2a**).

A solution of 2,3-dihydro-1*H*-isoindole (**3**) (5.87 g, 0.049 mole) and 4-chloropyridine hydrochloride (**4**) (8.13 g, 0.054 mole) in 1-methyl-2-pyrrolidinone (30 ml) was heated at 130° for 2 hours. The reaction was then added to water, and the mixture was extracted with ethyl acetate. The combined extracts were dried (sodium carbonate) and evaporated to give a solid that was filtered off, rinsed with water, dried and then passed through a column of florisil (5% methanol/ethyl acetate) to give, after evaporation of the product-containing fractions, 2.78 g (29%) of a tan solid. Compound **2a** was further purified as its maleate salt by recrystallization from methanol (charcoal treatment) giving colorless crystals (overall yield 11%), mp 229° dec; ^{1}H nmr (DMSO-d_6): δ 4.93 (s, 4H, aliphatic), 6.03 (s, 2H, maleate), 6.98 (d, J = 7 Hz, 2H, H-3, H-5 pyridine), 7.42 (m, 4H, aromatic), 8.36 (d, J = 7 Hz, 2H, H-2, H-6 pyridine); ms: m/z 196 (M^+). See Table 1 for analytical data.

2,3-Dihydro-2-(3-fluoro-4-pyridinyl)-1*H*-isoindole Maleate (**2b**).

With the exception of the use of *N,N*-dimethylformamide as the reaction solvent, compound **2b** was prepared analogously to compound **2a**. The free base of compound **2b** was purified via flash chromatography (14%) (50% ethyl acetate/dichloromethane) and further purified by recrystallization of its maleate salt from methanol/ethyl ether giving a colorless powder (8% overall yield), mp 204° dec; ^{1}H nmr (DMSO-d_6): δ 5.04 (d, J = 3 Hz, 4H, aliphatic), 6.12 (s, 2H, maleate), 7.00 (dd, J = 7,8 Hz, 1H, H-5 pyridine), 7.40 (m, 4H, aromatic), 8.26 (d, J = 7 Hz, 1H, H-6 pyridine), 8.56 (d, J = 8 Hz, 1H, H-2 pyridine); ms: m/z 214(M^+). See Table 1 for analytical data.

Method B.

2,3-Dihydro-3-hydroxy-3-methyl-2-(4-pyridinyl)-1*H*-isoindol-1-one (**6a**).

A solution of 2-(4-pyridinyl)-1*H*-isoindole-1,3-(2*H*)-dione (**5**) (8.08 g, 0.036 mole) in tetrahydrofuran (250 ml) was treated with a solution of methyl magnesium bromide in ether (14.4 ml of 3.0 *M*, 0.0432 mole). This solution was stirred for 1 hour at ambient temperature and quenched with a saturated solution of ammonium chloride. The mixture was diluted with ethyl acetate and water, and then the organic phase was separated, washed with water and saturated sodium chloride and then dried (magnesium sulfate). Removal of the solvents *in vacuo* afforded 7.2 g (83%) of **6a** as a white powder, which was further purified as its fumarate salt giving, after recrystallization from ethyl acetate/heptane, a colorless solid (40% overall yield), mp 213° dec; ^{1}H nmr (DMSO-d_6): δ 1.68 (s, 3H, CH_3), 6.63 (s, 2H, fumarate), 7.20 (br s, 1H, O*H*), 7.62 (m, 1H, aromatic), 7.78 (m, 3H, aromatic), 7.91 (d, J = 7 Hz, 2H, H-3,H-5 pyridine), 8.62 (d, J = 7 Hz, 2H, H-2,H-6 pyridine); ms: m/z 240 (M^+).

Anal. Calcd. for $C_{14}H_{12}N_2O_2 \cdot C_4H_4O_4$: C, 60.67; H, 4.53; N, 7.86. Found: C, 60.74; H, 4.35; N, 7.78.

Compounds **6b-f** were synthesized in an analogous manner.

2,3-Dihydro-3-methylene-2-(4-pyridinyl)-1*H*-isoindol-1-one (**8a**).

A mixture of compound **6a** (10.2 g, 0.0425 mole) and phosphorus pentoxide (6.03 g, 0.0425 mole) was heated under vacuum (0.5 mm) at 200° for 20 minutes. Iced water was then added, the mixture was made basic with aqueous potassium carbonate solution, and the resulting solid was filtered and purified by passing through a column of florisil (ethyl acetate) to give 6.23 g (66%) of a brown solid. A portion was further purified (45% overall yield) by recrystallization from methanol giving **8a** as reddish-brown platelets, mp 173-174°; ^{1}H nmr (DMSO-d_6): δ 5.02 (d, J = 2 Hz, 1H, C=CH_2), 5.67 (d, J = 2 Hz, 1H, C=CH_2), 7.54 (d, J = 7 Hz, 2H, H-3,H-5 pyridine), 7.78 (m, 3H, aromatic), 8.15 (d, J = 7 Hz, 1H, aromatic), 8.79 (d, J = 7 Hz, 2H, H-2,H-6 pyridine); ms: m/z 222 (M^+).

Anal. Calcd. for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N 12.60. Found: C, 75.48; H, 4.46; N, 12.72.

Compound **8b** was synthesized in an analogous manner as a mixture of syn and anti isomers.

2,3-Dihydro-3-methyl-2-(4-pyridinyl)-1*H*-isoindol-1-one (**9a**).

A solution of compound **8a** (4.22 g, 0.019 mole) in tetrahydrofuran (200 ml) was added to a suspension of 10% Pd on carbon (0.95 g) in tetrahydrofuran (50 ml). The reaction vessel was pressurized with 45 psi of hydrogen gas and was shaken for 6 hours. Filtration of the catalyst followed by concentration of the solvent *in vacuo* gave 3.85 g of **9a** (91%). A portion was further purified as its maleate salt by crystallization from methanol/ether giving white platelets (74% overall yield), mp 149° dec; ^{1}H nmr (DMSO-d_6): δ 1.52 (d, J = 7 Hz, 3H, CHCH_3), 5.64 (q, J = 7 Hz, 1H, C*H*CH$_3$), 6.22 (s, 2H, maleate), 7.61 (m, 1H, aromatic), 7.83 (m, 3H, aromatic), 8.04 (d, J = 7 Hz, 2H, H-3,H-5 pyridine), 8.72 (d, J = 7 Hz, 2H, H-2,H-6 pyridine); ms; m/z 224 (M^+).

Anal. Calcd. for $C_{14}H_{12}N_2O \cdot C_4H_4O_4$: C, 63.53; H,4.74; N, 8.23. Found: C, 63.52; H, 4.63; N, 8.14.

Compound **9b** was synthesized in an analogous manner.

2,3-Dihydro-1-methyl-2-(4-pyridinyl)-1H-isoindole Fumarate (**2c**).

A solution of compound **9a** (1.34 g, 0.060 mole) in tetrahydrofuran (50 ml) was treated with a 1 Molar solution of lithium aluminum hydride in tetrahydrofuran (7.2 ml). This was stirred at ambient temperature for 20 minutes. The reaction was then quenched by the dropwise addition of a saturated aqueous solution

of ammonium chloride, the mixture was diluted with ethyl acetate and the inorganic salts were filtered and rinsed with ethyl acetate. The organics were dried and the solvent was removed *in vacuo* to give 1.19 g of 2,3-dihydro-1-hydroxy-3-methyl-2-(4-pyridinyl)-1H-isoindole (**10a**) in 88% yield. Compound **10a** was used in the next step without further purification.

A solution of compound **10a** (1.19 g, 0.053 mole) in dichloromethane (20 ml) was treated with trifluoroacetic acid (8 ml) followed by triethylsilane (1.16 ml, 0.072 mole). After stirring for 10 minutes the reaction was added to a dilute potassium carbonate solution and extracted with ethyl acetate. The organic material was washed with water, dried and concentrated *in vacuo* to give **2c** as an oil in 66% yield. Compound **2c** was further purified as its fumarate salt (19% overall yield) after recrystallization from ethanol/ethyl acetate giving a white powder, mp 185° dec; ^{1}H nmr (DMSO-d_6): δ 1.44 (d, J = 7 Hz, 3H, CH_3), 4.65 (d, J = 14 Hz, 1H, H-3), 4.82 (dd, J = 1.14 Hz, 1H, H-3), 5.28 (dq, J = 1.7 Hz, 1H, H-1), 6.60 (s, 2H, fumarate), 6.78 (d, J = 8 Hz, 2H, H-3,H-5 pyridine) 7.40 (m, 4H, aromatic), 8.23 (d, J = 8 Hz, 2H, H-2,H-6 pyridine); ms: m/z 210 (M$^+$).

Compound **2d** was synthesized in an analogous manner. See Table 1 for analytical results.

Method C.

2,3-Dihydro-1-propyl-2-(4-pyridinyl)-1*H*-isoindole Maleate (**2e**).

A solution of compound **6c** (7.0 g, 0.026 mole, prepared as in method B) in tetrahydrofuran (150 ml) was added to a chilled mixture of lithium aluminum hydride (52.2 ml of a 1 Molar solution in tetrahydrofuran) and aluminum chloride (2.32 g, 0.017 mole). The reaction was stirred for 30 minutes and then quenched by the dropwise addition of a saturated aqueous solution of ammonium chloride. The mixture was diluted with ethyl acetate, and then the inorganics salts were filtered and rinsed with ethyl acetate, the organic material was dried and the solvent was removed *in vacuo*. The desired compound was purified *via* flash chromatography (50% ethyl acetate/dichloromethane) to give 2.94 g (47%) of **2e** as an oil which was further purified as its maleate salt (34% overall yield) after crystallization from methanol, giving an off-white powder, mp 142° dec; ^{1}H nmr (DMSO-d_6) δ 0.78 (t, J = 7 Hz, 3H, $(CH_2)_2CH_3$), 1.04 (m, 2H, CH_2CH_3), 1.98 (m, 2H, $CH_2CH_2CH_3$), 4.90 (s, 2H, H-3), 5.54 (m, 1H, H-1), 6.04 (s, 2H, maleate), 7.08 (d, J = 8 Hz, 2H, H-3,H-5 pyridine), 7.42 (m, 4H, aromatic), 8.35 (d, J = 8 Hz, 2H, H-2,H-6 pyridine); ms: m/z 238 (M$^+$). See Table 1 for analytical results.

2,3-Dihydro-1-hydroxy-1-phenyl-2-(4-pyridinyl)-1*H*-isoindole (**7**).

A solution **6f** (5.76g, 0.019 mole, prepared as in method B) in tetrahydrofuran (170 ml) was reduced as for **6c** above to give, after recrystallization from methanol/water, 3.08g (57%) of **7**, mp 172-174°; ^{1}H nmr (DMSO-d_6): δ 4.80 (d, 1H, J = 14 Hz, CH_2), 4.96 (d, 1H, J = 14Hz, CH_2), 6.63 (d, 2H, J = 6 Hz, H-3, H-5 pyridine), 6.47 (s, 1H, exchanges with deuterium oxide, OH), 6.5-6.8 (m, 9H, aromatic), 8.02 (d, 2H, J = 6 Hz, H-2, H-6 pyridine); ms: m/z 288 (M$^+$).

Anal. Calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.71. Found: C, 78.94; H, 5.68; N, 9.63.

2,3-Dihydro-1-phenyl-2-(4-pyridinyl)-1*H*-isoindole Maleate (**2h**).

A solution of **7** (2.80 g, 0.10 mole) in dichloromethane (60 ml) was reduced as for **10a** above to give, after trituration with diethyl ether, salt formation and crystallization from methanol/diethyl ether, 1.80 g (46%) of **2i**, mp 164-166°; ^{1}H nmr (DMSO-d_6): δ 5.10 (d, 1H, J = 14 Hz, CH_2), 5.38 (d, 1H, J = 14 Hz, CH_2), 6.02 (s, 2H, maleate), 6.42 (s, 1H, H-1), 6.90 (d, 2H, J = 6 Hz, H-3, H-5 pyridine), 6.2-6.6 (m, 9H, aromatic), 8.30 (d, 1H, J = 6 Hz, H-2, H-6 pyidine); ms: m/z 272 (M$^+$). See Table 1 for analytical results.

2-(1-Benzyl-4-piperidinyl)-2,3-dihydro-1-ethyl-1*H*-isoindole Dimaleate (**2i**).

A solution of 2-(1-benzyl-4-piperidinyl)-2,3-dihydro-1-ethyl-3-hydroxyisoindol-1-one (4.35 g, 0.012 mole, prepared as in method B from 1-benzyl-4-phthalimidopiperidine [7]) in tetrahydrofuran (50 ml) was reduced as for **6c** above to give, after flash chromatography (ethyl acetate), salt formation, and crystallization from methanol/diethyl ether, 2.88 g (43%) of **2i**, mp 180° dec; ^{1}H nmr (DMSO-d_6): δ 0.88 (t, J = 7 Hz, 3H, CH_2CH_3), 1.90 (m, 4H, 3- and 5-CH_2 piperidine) 2.04 (m, 2H, CH_2CH_3), 2.85 (m, 2H, H-2, H-6 piperidine), 3.38 (m, 3H, H-2, H-4, H-6 piperidine), 4.20 (s, 2H, $C_6H_5CH_2$), 4.40 (m, 2H, H-3), 4.65 (m, 1H, H-3), 6.10 (s, 4H, maleate), 7.35 (m, 4H, isoindoline), 7.44 (m, 5H, $C_6H_5CH_2$); ms: m/z 320 (M$^+$). See Table 1 for analytical results.

Acknowledgement.

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