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PROBES FOR NARCOTIC RECEPTOR MEDIATED PHENOMENA. 38.[1] AN EXPEDITIOUS SYNTHESIS OF *RAC-CIS*-4a-ETHYL-2-METHYL-1,2,3,4,4a,9a-HEXAHYDROBENZOFURO[2,3-*c*]PYRIDIN-6-OL AND *RAC-CIS*-2-METHYL-4a-PHENETHYL-1,2,3,4,4a,9a-HEXAHYDROBENZOFURO[2,3-*c*]PYRIDIN-6-OL

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This paper is dedicated to the memory of Dr. John Daly, an exceptional scientist and our colleague for over 30 years at NIDDK, NIH.

Abstract - A high-yielding five-step synthesis of *cis*-benzofuropyridin-6-ols provided an improved route to compounds with low to subnanomolar affinity at opioid receptors and high antinociceptive potency. This synthesis provided the known *rac-cis*-4a-ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol (**1a**) in high yield, and the novel *rac-cis*-2-methyl-4a-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol (**1b**). It was achieved using NBS to prepare the key intermediate **7**. Di-demethylation followed by subsequent displacement of the bromine by the phenolic ion in hot Et_3N gave the desired **1a**. The structure of **1a** was confirmed by X-ray crystallography.

INTRODUCTION

As part of our continuing study of the relationship between the three-dimensional structure of ligands that

interact with opioid receptors and their pharmacological effects, we have pursued the synthesis of a number of hexahydrobenzofuropyridinols[2] (e.g., **1a** and **1b**) that are structurally related to members of the class of oxide-bridged 5-phenylmorphans **2a** through **2f**.[1,3] The oxide-bridged 5-phenylmorphans compounds are structurally rigid and were based on the 5-phenylmorphan opioids originated by May et al.,[4] some of which have been found to interact with high affinity at μ or δ opioid receptors as agonists or antagonists.[5]

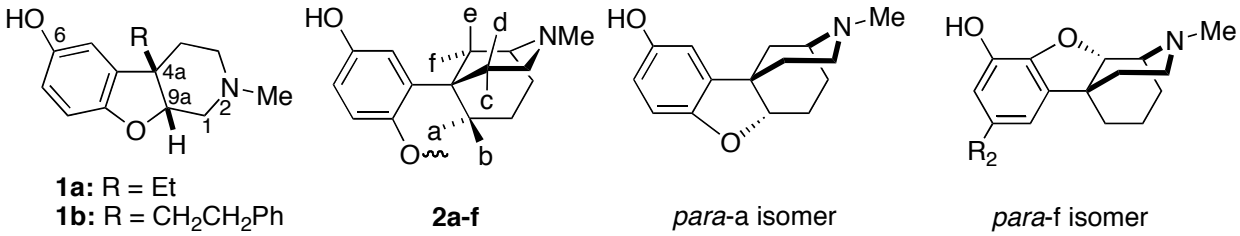
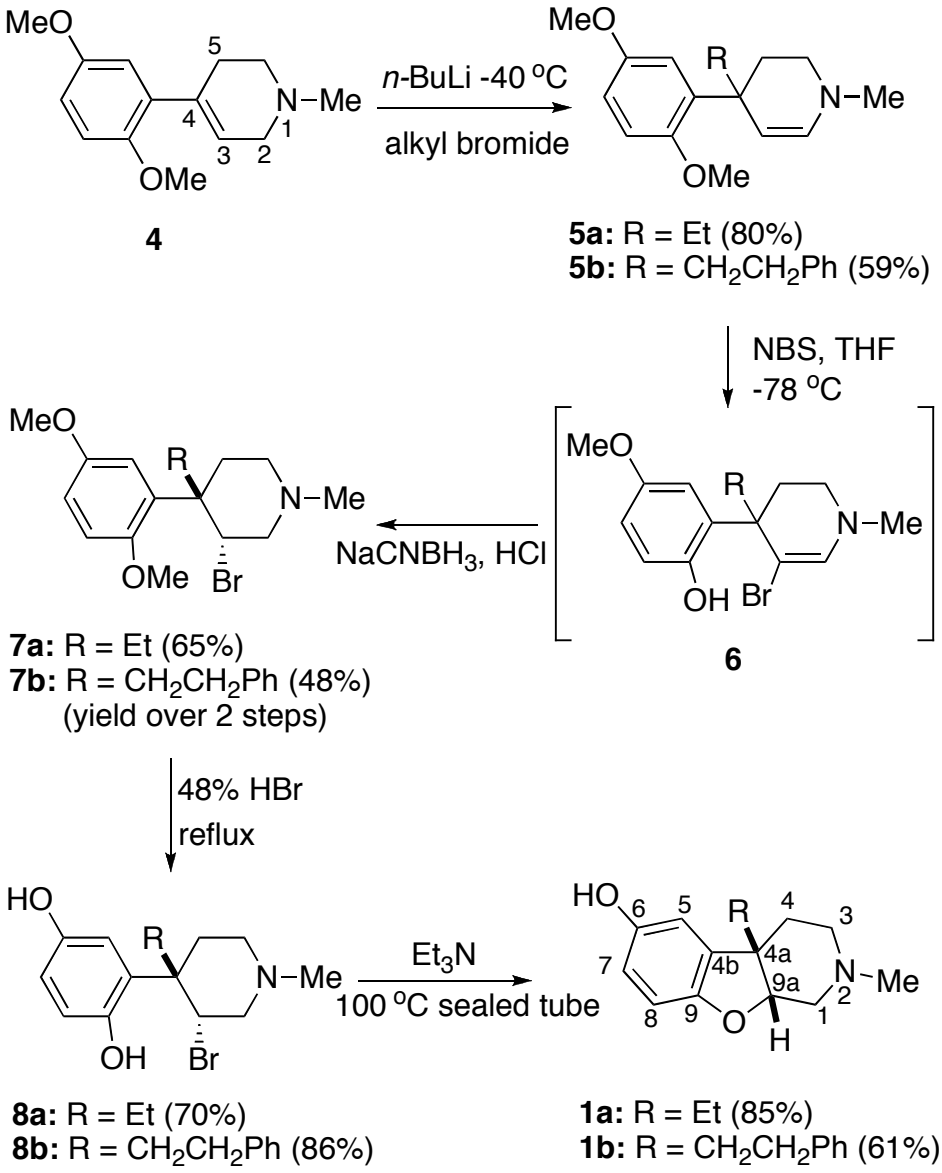


Figure 1. Hexahydrobenzofuro[2,3-c]pyridin-6-ols and the *para*-hydroxy a-f oxide-bridged phenylmorphans

Hexahydrobenzofuropyridinols can be considered as congeners of the 5-phenylmorphans and are in fact partial structures of oxide-bridged phenylmorphans **2a-f**. *N*-substituted *rac*-*cis*-benzofuro[2,3-*c*]pyridin-6-ols (e.g., 4a-ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol, **1a**) have been shown by Hutchison et al.,[2] to have high affinity for opioid-receptors and possess significant antinociceptive activity. Because of our interest in structurally rigid compounds that interact with opioid receptors, we have developed a concise and efficient synthesis for 4a-ethyl (**1a**) and 4a-phenethyl (**1b**) analogues of *rac*-*cis*-*N*-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol. This short simple synthesis enables the preparation of a variety of analogues of *N*-substituted 4a-alkyl or aralkyl analogues of hexahydrobenzofuro[2,3-*c*]pyridin-6-ols.

RESULTS AND DISCUSSION

The synthetic approach to **1**, shown in Scheme 1 contains two important steps: introduction of the desired R-group to give the intermediate **5** and subsequent formation of the oxide bridge to form the final product. A useful feature of this route is the well precedented synthesis of enamine moiety **5** based on the method of Evans[6] and utilized in our oxide-bridged phenylmorphan syntheses.[3c-f, 3j] With the necessary enamine in hand, additional functionalization needed to close the oxide-bridge can be achieved with relative ease.



Scheme 1. New synthetic route to hexahydrobenzofuro[2,3-*c*]pyridin-6-ols

A large amount of the known tetrahydropyridine[3d] **4** was prepared (caution - a related tetrahydropyridine was noted to have neurotoxic effects),[7a-b] and metalation of **4** was achieved using *n*-butyllithium at -40 °C. Quenching of the anion with bromoethane gave the enamine **5a** in excellent yields. In a departure from previous reports,[3d,3j] NBS instead of NBA was used to introduce bromine at C-3. Bromination followed by an immediate reduction of the intermediate with $NaCNBH_3$ gave **7a** as a pure solid. The structural assignment of the reduction product rests on a single crystal X-ray determination of the HBr salt of **7a** that showed that the ethyl and the bromo group bear a *trans* relationship (Figure 2).

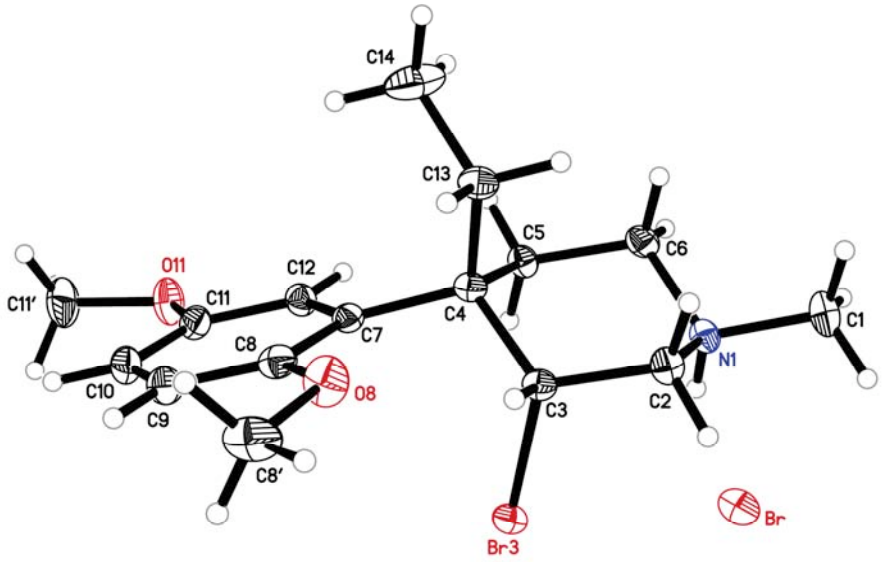


Figure 2. X-Ray crystallographic structure of 3-bromo-4-(2,5-dimethoxyphenyl)-4-ethyl-1-methylpiperidine hydrobromide (**7a**•HBr). Displacement ellipsoids are shown at the 50% level.

Prior to oxide bridge formation, it was important to remove both of the methyl protecting groups on the aromatic oxygen atoms. Initial attempts at deprotection using BBr_3 in refluxing chloroform was marred by the loss of only one of the methyl groups, and solubility issues. Switching to 48% HBr under reflux conditions gave the desired deprotected diol **8a** as an HBr salt. X-Ray crystallography on **8a** indicated that the ethyl and bromo group still maintained a *trans* relationship (Figure 3).

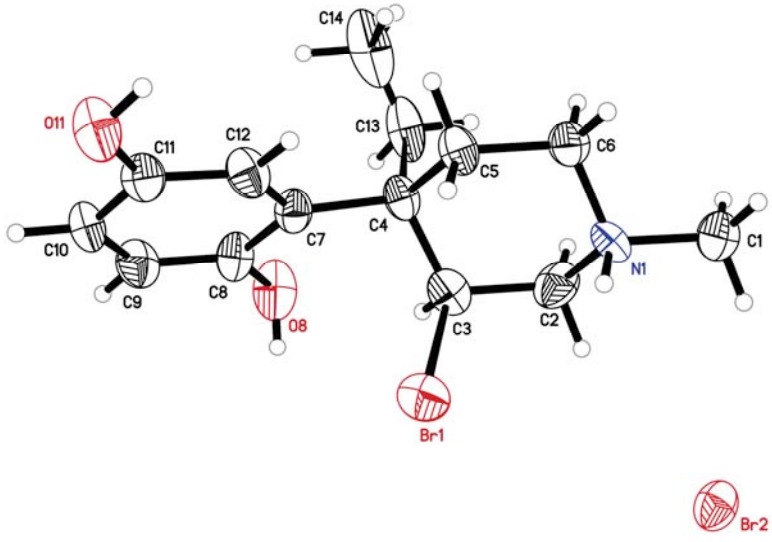


Figure 3. X-Ray crystallographic structure of 2-(3-bromo-4-ethyl-1-methylpiperidin-4-yl)benzene-1,4-diol hydrobromide (**8a**•HBr). Displacement ellipsoids are shown at the 50% level.

Compound **8a** was now ready for the final step, oxide bridge formation to give **1a**. This was first attempted by treating the HBr salt of **8a** with cold methanolic NaOH. Although this transformation gave **1a** as the major product, additional products, possibly the *trans* compound (ca 5%) and other unidentified materials along with decomposition products resulted in a low (~ 40%) yield. That the reaction failed to deliver better and more consistent yields was disconcerting. After unsuccessfully trying reagents such as t-BuOK, NaOEt and NaH to bring about the oxide ring closure, attention was turned to Et_3N to facilitate ring closure. It was indeed gratifying to observe the formation of the desired ring closure product upon treatment of **8a**•HBr in refluxing Et_3N (59% yield). Though some unreacted starting material and Et_3N•HBr were found, the reaction behaved consistently in refluxing Et_3N. It was interesting to note that **8a** proceeded to give **1a** with retention of the relative stereochemistry. That the transformation gave the *cis*-isomer of product **1a** was confirmed by single crystal X-ray determination (Figure 4) and NOESY analysis. This seems to rule out a simple SN_2 type mechanism for the ring formation.

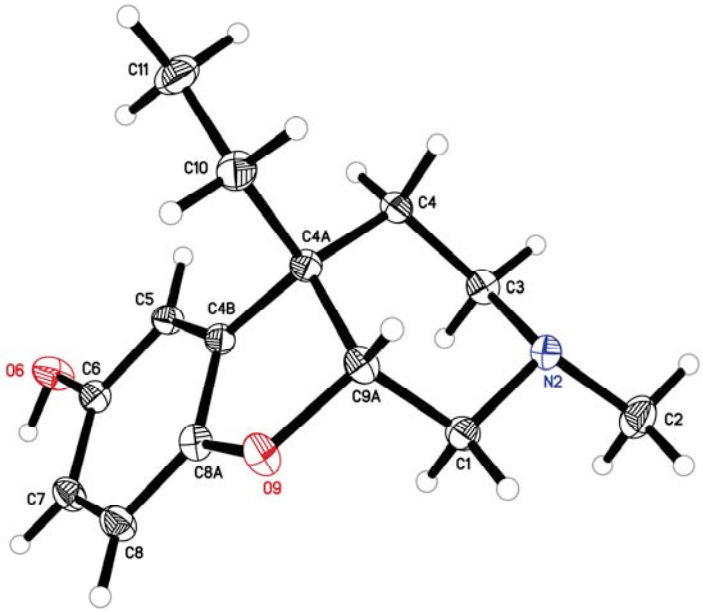


Figure 4. X-Ray crystallographic structure of 4a-ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol (**1a**). Displacement ellipsoids are shown at the 50% level.

The yield of **1a** was further improved by using compound **8a** as a base, not as the HBr salt. Heating **8a** and dry Et_3N in a sealed tube at 100 °C gave **1a** in 85% yield after purification by column chromatography. Using methanol as a co-solvent resulted in oxide-bridge formation with a lower (56%) yield.

A brief effort to demonstrate the utility of this route was undertaken by focusing on the synthesis of *rac*-

cis-2-methyl-4a-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol (**1b**, Scheme 1). Addition of 2-bromoethylbenzene to the metalated **4** gave compound **5b** in reasonable yield. The two-step addition/reduction protocol using NBS/$NaCNBH_3$ gave **7b** in modest yield over two steps. The relative stereochemistry of this bromo compound was assigned by correlation of spectral data with **7a** and NOESY studies. Di-demethylation in refluxing HBr followed by heating the free base of **8b** with Et_3N in a sealed tube uneventfully gave compound **1b** as a single compound with *cis*-stereochemistry as determined by 2-dimensional NMR spectral data. A small amount of methanol (1 mL) was used with the Et_3N (15 mL) to solubilize **8b**. That amount of methanol did not appear to effect the yield of **1b**.

CONCLUSION

The simple concise synthesis of **1a** and **1b** represents a facile approach to the preparation of a variety of partial structures of oxide-bridged phenylmorphans. The new compounds will be pharmacologically evaluated and the data used to examine the spatial relationship of hexahydrobenzofuro[2,3-*c*]pyridin-6-ols to the oxide-bridged phenylmorphans and to other classes of structurally related opioids. The findings from the pharmacological and the quantum chemical topological studies will be reported in due course.

EXPERIMENTAL

General

Mass spectra (CIMS) were obtained using a Finnigan 4600 mass spectrometer unless otherwise noted. ^1H NMR (500 MHz) were recorded on a Bruker Avance 500 instrument in deuterated solvents (Cambridge Isotope Laboratories, Inc.) as specified. TMS was used as an internal standard. IR spectra were recorded on a Beckman IR 4230 spectrometer. Column chromatography was performed using 230-400-mesh EM silica gel. Melting points were determined on a Buchi B-545 melting point apparatus and are uncorrected. Combustion analyses were determined at Atlantic Microlabs, Atlanta, GA.

4-(2,5-Dimethoxyphenyl)-4-ethyl-1-methyl-1,2,3,4-tetrahydropyridine (5a)

A solution of **4** (20.0 g, 85.8 mmol)[7] (Caution – a structurally related compound was reported to have neurotoxic activity)[7] in dry THF (200 mL) was stirred under argon at -40 °C. A solution of *n*-butyllithium, 2.5 M in hexane (69.0 mL, 172 mmol), was added, producing a deep red color. The mixture was stirred at -40 °C for 2 h. Bromoethane (12.8 mL, 172 mmol) was added, producing a yellow solution, which was then stirred and brought to 20 °C over 1 h. The reaction mixture was then treated with a saturated aqueous NH_4Cl solution (20 mL). The reaction mixture was partitioned between Et_2O (2 X 200 mL) and H_2O (200 mL). The organic layer was dried over anhydrous Na_2SO_4 and the organic solvent was removed in vacuo to give an orange oil. Column chromatography of the crude material using 10% hexanes in ether gave

18.0 g (80%) of **5a** as a pure yellow oil. IR ($CHCl_3$) 2935 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.01 (d, 1H, *J* = 3.0 Hz), 6.77 (d, 1H, *J* = 8.5 Hz), 6.67 (dd, 1H, *J* = 3.0 and 8.5 Hz), 5.92 (d, 1H, *J* = 8.0 Hz), 4.65 (d, 1H, *J* = 8.0 Hz), 3.77 (s, 3H), 3.75 (s, 3H), 2.73 (m, 1H), 2.54 (s, 3H), 2.47 (m, 2H), 2.19 (m, 1H), 1.86 (dt, 1H, *J* = 2.0 and 12.0 Hz), 1.65 (m, 1H), 0.63 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.79, 151.89, 137.72, 136.22, 119.88, 111.87, 109.88, 104.41, 55.50 (2C), 47.11, 42.41, 41.27, 33.36, 32.31, 9.02; HRMS (TOF MS ES^+) calcd for $C_{16}H_{24}NO_2$ $(M + H)^+$ 262.1807, found: 262.1813. Anal. Calcd for $C_{16}H_{23}NO_2$: C, 73.53; H, 8.87; N, 5.36. Found: C, 73.42; H, 8.89; N, 5.08.

3-Bromo-4-(2,5-dimethoxyphenyl)-4-ethyl-1-methylpiperidine (7a)

To a solution of **5a** (7.0 g, 27.0 mmol) in dry THF (50 mL) at -78 °C was added N-bromosuccinimide (4.7 g, 27.0 mmol) in dry THF (20 mL). The mixture was stirred at 20 °C for 1 h and the solvent removed to give an orange oil. The crude product was dissolved in MeOH (50 mL) and 37% HCl (1 mL) was added to the suspension. To this suspension was added solid $NaBH_3CN$ (1.7 g, 27.0 mmol) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was then diluted with aqueous saturated $NaHCO_3$ and the organic layer was washed with H_2O (30 mL) and extracted into CH_2Cl_2 (100 mL). Removal of the solvent in vacuo gave a brown oil. Purification of the crude product by column chromatography using 30% hexanes in Et_2O gave a yellow solid (6.0 g, 65% over two steps). A small batch of the yellow solid was dissolved in MeOH and treated with 48% HBr to give white crystals of **7a**•HBr, mp 220-223 °C. IR ($CHCl_3$) 2938 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.78 (d, 1H, *J* = 8.5 Hz), 6.71 (dd, 1H, *J* = 2.5 and 8.5 Hz), 6.69 (d, 1H, *J* = 2.0 Hz), 5.44 (s, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 3.03 (d, 1H, *J* = 13.5 Hz), 2.89 (d, 1H, *J* = 11.0 Hz), 2.81 (d, 1H, *J* = 12.8 Hz), 2.41 (dt, 1H, *J* = 2.5 and 12.5 Hz), 2.33 (s, 3H), 2.28 (t, 1H, *J* = 11.5 Hz), 2.06 (m, 1H), 1.93 (m, 1H), 1.86 (d, 1H, *J* = 12.5 Hz), 0.50 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.03, 152.51, 135.66, 115.83, 111.79, 110.04, 58.52 (2C), 55.89, 55.48, 51.11, 46.16, 44.79, 26.77, 23.87, 9.55; HRMS (TOF MS ES^+) calcd for $C_{16}H_{25}Br^{79}NO_2$ $(M + H)^+$ 342.1069, found: 342.1055. Anal. Calcd for $C_{16}H_{24}BrNO_2$•HBr: C, 45.41; H, 5.95; N, 3.31. Found: C, 44.95; H, 5.99; N, 3.26.

2-(3-Bromo-4-ethyl-1-methylpiperidin-4-yl)benzene-1,4-diol (8a)

To compound **7a** (5.7 g, 16.7 mmol) was added 48% HBr (20 mL) and the emulsion was refluxed for 10 h. After completion of the reaction, the excess HBr was removed by distillation to leave **8a**•HBr as a white solid (4.6 g, 70%). A small batch was recrystallized from MeOH to give white crystals of **8a**•HBr, mp 248-251 °C. IR ($CHCl_3$) 3020 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 6.62 (d, 1H, *J* = 8.5 Hz), 6.57 (dd, 1H, *J* = 2.5 and 8.5 Hz), 6.46 (d, 1H, *J* = 2.0 Hz), 5.94 (s, 1H), 4.02 (d, 1H, *J* = 14.0 Hz), 3.79 (d, 1H, *J* = 14.0 Hz), 3.55 (d, 1H, *J* = 12.5 Hz), 3.40 (t, 1H, *J* = 12.5 Hz), 2.99 (s, 3H), 2.46 (m, 2H), 2.24 (d, 1H, *J* = 14.0 Hz), 2.03 (m, 1H) 0.60 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 150.72, 149.79,

131.54, 117.55, 115.85, 115.18, 57.95, 55.13, 51.79, 44.13, 44.10, 25.76, 23.78, 10.03; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{21}BrNO_2$ $(M + H)^+$ 314.0756, found: 314.0755. Anal. Calcd for $C_{14}H_{20}BrNO_2$•HBr: C, 42.56; H, 5.36; N, 3.54. Found: C, 42.26; H, 5.41; N, 3.48.

4a-Ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol (1a)

Compound **8a** (0.80 g, 2.54 mmol) (free base was obtained after neutralization of the HBr salt of **8a** by partitioning between $NaHCO_3$ and $CHCl_3$) was treated with excess Et_3N (15 mL). The reaction mixture was placed in a sealed tube and heated at 100°C for 3 h. Cooling of the reaction mixture, followed by evaporation of the excess Et_3N gave a brown solid. This solid chromatographed on a silica-gel column and the desired product **1a** was eluted using 15% MeOH in CH_2Cl_2 to give an off-white solid (504 mg, 85%), mp 178-180 °C. IR ($CHCl_3$) 3020 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.65 (d, 1H, *J* = 8.0 Hz), 6.59 (d, 2H, *J* = 9.5 Hz), 4.48 (t, 1H, *J* = 5.5 Hz), 2.85 (dd, 1H, *J* = 4.0 and 11.5 Hz), 2.54 (dd, 1H, *J* = 5.0 and 10.0 Hz), 2.37 (dd, 1H, *J* = 7.0 and 12.0 Hz), 2.30 (s, 3H), 2.18 (t, 1H, *J* = 10.0 Hz), 2.01 (d, 1H, *J* = 14.0 Hz), 1.83 (t, 1H, *J* = 10.5 Hz), 1.68 (m, 1H), 1.55 (m, 1H), 0.81 (t, 3H, *J* = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.53, 150.41, 134.56, 114.63, 111.02, 110.75, 84.14, 56.05, 51.85, 46.15, 46.00, 32.00 (2C), 8.55; HRMS (TOF MS ES$^+$) calcd for $C_{14}H_{20}NO_2$ $(M + H)^+$ 234.1494, found: 234.1498. Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.85; H, 8.10; N, 6.00.

4-(2,5-Dimethoxyphenyl)-1-methyl-4-phenethyl-1,2,3,4-tetrahydropyridine (5b)

5b was prepared from **4** (10.0 g, 42.9 mmol) (Caution – a structurally related compound was reported to have neurotoxic activity)[7], a solution of *n*-butyllithium, 2.5 M in hexane (34.5 mL, 85.8 mmol) and phenethyl bromide (11.7 mL, 85.8 mmol), as noted with **5a**, to give 8.6 g (59%) of **5b** as a pure yellow oil. IR ($CHCl_3$) 2937, 1493 cm^1; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.52 (t, 2H, *J* = 7.5 Hz), 7.12 (d, 1H, *J* = 7.0 Hz), 7.09 (m, 3H), 6.80 (d, 1H, *J* = 8.5 Hz), 6.71 (dd, 1H, *J* = 3.5 and 9.0 Hz), 5.99 (d, 1H, *J* = 8.0 Hz), 4.75 (d, 1H, *J* = 7.5 Hz), 3.80 (s, 3H), 3.78 (s, 3H), 2.75 (dd, 1H, *J* = 3.0 and 7.0 Hz), 2.57 (s, 3H), 2.44-2.51 (m, 4 H), 2.19 (dt, 1H, *J* = 4.0 and 12.5 Hz), 1.91 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 152.94, 151.97, 143.83, 137.47, 136.56, 128.47 (2C), 128.26 (2C), 125.40, 120.06, 111.80, 110.55, 104.27, 55.71, 55.52, 47.08, 42.54, 42.28, 41.16, 33.94, 31.47; HRMS (TOF MS ES$^+$) calcd for $C_{22}H_{28}NO_2$ $(M + H)^+$ 338.2120, found: 338.2124.

3-Bromo-4-(2,5-dimethoxyphenyl)-1-methyl-4-phenethylpiperidine (7b)

To a solution of **5b** (5.0 g, 14.8 mmol) in dry THF (40 mL) at -78 °C was added N-bromosuccinimide (2.6 g**,** 14.8 mmol) in dry THF (15 mL). The reaction was carried out as with **7a** to give a brown oil. The crude product was dissolved in MeOH (50 mL) and 37% HCl (1 mL) was added. Solid $NaBH_3CN$ (0.93 g, 14.8 mmol) was then added and the reaction continued as with **7a**. The organic layer was washed with H_2O (30 mL) and extracted into CH_2Cl_2 (100 mL). Evaporation of the solvent gave a brown oil.

Purification of the crude product by column chromatography using 30% hexanes in Et_2O gave white crystalline solid **7b** (3.0 g, 48% over two steps), mp 134-136 °C. IR ($CHCl_3$) 2941 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 7.24 (t, 2H, *J* = 7.5 Hz), 7.17 (t, 1H, *J* = 7.5 Hz), 7.02 (d, 2H, *J* = 7.5 Hz), 6.86 (d, 1H, *J* = 7.5 Hz), 6.78 (m, 2H), 5.46 (s, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.05 (d, 1H, *J* = 13.5 Hz), 2.99 (d, 1H, *J* = 11.5 Hz), 2.82 (d, 1H, *J* = 13.5 Hz), 2.56 (dt, 1H, *J* = 3.0 and 10.0 Hz), 2.43 (m, 2H), 2.36 (s, 3H), 2.33 (m, 1H), 2.22 (dt, 1H, *J* = 4.5 and 12.5 Hz), 2.00 (d, 1H, *J* = 13.0 Hz), 1.93 (dt, 1H, *J* = 3.5 and 12.5 Hz); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 153.23, 152.53, 142.56, 135.52, 128.34 (2C), 128.24 (2C), 125.74, 115.67, 111.92, 110.42, 58.36, 58.15, 55.90, 55.53, 51.12, 46.10, 44.55, 33.76, 31.97, 27.45; HRMS (TOF MS ES$^+$) calcd for $C_{22}H_{29}Br^{81}NO_2$ $(M + H)^+$ 420.1316, found: 420.1356. Anal. Calcd for $C_{22}H_{28}BrNO_2$: C, 63.16; H, 6.75; N, 3.35. Found: C, 63.32; H, 6.63; N, 3.31.

2-(3-Bromo-1-methyl-4-phenethylpiperidin-4-yl)benzene-1,4-diol (8b)

To **7b** (2.0 g, 4.8 mmol) was added 48% HBr (20 mL) and the emulsion was refluxed for 10 h. After completion of the reaction, the excess HBr was removed by distillation to leave **8b**•HBr as a light brown solid. Neutralization of the HBr salt by partitioning between $NaHCO_3$ and $CHCl_3$ gave 1.6 g (86%) of **8b**. A small batch of **8b**•HBr was recrystallized from MeOH to give white crystals of **8b**•HBr, mp 226-228 °C. IR ($CHCl_3$) 3020 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 7.21 (t, 2H, *J* = 7.5 Hz), 7.12 (d, 1H, *J* = 7.5 Hz), 7.07 (d, 2H, *J* = 7.0 Hz), 6.69 (d, 1H, *J* = 8.0 Hz), 6.62 (dd, 1H, *J* = 2.5 and 8.5 Hz), 6.54 (d, 1H, *J* = 2.0 Hz), 5.92 (s, 1H), 3.99 (d, 1H, *J* = 14.5 Hz), 3.76 (d, 1H, *J* = 14.0 Hz), 3.58 (d, 1H, *J* = 12.5 Hz), 3.48 (t, 1H, *J* = 10.5 Hz), 2.98 (s, 3H), 2.70 (dt, 1H, *J* = 3.0 and 12.0 Hz), 2.55 (dt, 1H, *J* = 3.00 and 11.0 Hz), 2.41 (dt, 1H, *J* = 5.5 and 12.5 Hz), 2.30 (m, 2H), 2.05 (dt, 1H, *J* = 3.5 and 12.5 Hz); ^{13}C NMR (CD_3OD, 125 MHz) δ 150.89, 149.82, 143.23, 131.65, 129.44 (2C), 129.32 (2C), 126.85, 117.69, 115.79, 115.46, 57.90, 54.96, 51.85, 44.92, 44.10, 33.47, 33.23, 26.39; HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{25}Br^{79}NO_2$ $(M + H)^+$ 390.1069, found: 390.1070. Anal. Calcd for $C_{20}H_{24}BrNO_2$•HBr•H_2O: C, 49.10; H, 5.56; N, 2.86. Found: C, 48.95; H, 5.92; N, 2.67.

2-Methyl-4a-phenethyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol (1b)

Compound **8b** (800 mg, 2.1 mmol) was treated with MeOH (1 mL) and excess Et_3N (15 mL). The reaction mixture was placed in a sealed tube and heated at 100°C for 3 h. Cooling of the reaction mixture, followed by evaporation of the excess Et_3N gave a brown solid. This solid was chromatographed using a silica-gel column and the desired product was eluted using 15% MeOH in CH_2Cl_2 to give an off-white solid **1b** (389 mg, 61%), mp 203-205 °C. IR ($CHCl_3$) 3055 cm^{-1}; ^1H NMR (CD_3OD, 500 MHz) δ 7.23 (t, 2H, *J* = 7.5 Hz), 7.13 (d, 1H, *J* = 7.5 Hz), 7.10 (d, 2H, *J* = 7.0 Hz), 6.66 (s, 1H), 6.63 (d, 1H, *J* = 8.5 Hz), 6.58 (d, 1H, *J* = 8.5 Hz), 4.48 (t, 1H, *J* = 5.5 Hz), 2.80 (dd, 1H, *J* = 5.0 and 12.5 Hz), 2.58 (dt, 1H, *J* = 5.0 and 13.0 Hz), 2.44-2.55 (m, 2H), 2.36 (dd, 1H, *J* = 7.0 and 12.5 Hz), 2.25 (s, 3H), 2.15 (dt, 1H, *J* =

2.5 and 11.0 Hz), 2.09 (m, 1H), 1.94 (dt, 1H, *J* = 5.0 and 13.5 Hz), 1.77-1.87 (m, 2H); ^{13}C NMR (CD_3OD, 125 MHz) δ 153.24, 152.90, 143.62, 135.48, 129.42 (2C), 129.27 (2C), 126.80, 115.42, 111.54, 111.44, 85.20, 57.15, 52.74, 46.93, 46.23, 42.68, 33.82, 31.69; HRMS (TOF MS ES$^+$) calcd for $C_{20}H_{24}NO_2$ $(M + H)^+$ 310.1807, found: 310.1803. Anal. Calcd for $C_{20}H_{23}NO_2 \cdot 0.25H_2O$: C, 76.52; H, 7.54; N, 4.46. Found: C, 76.30; H, 7.47; N, 4.56.

X-Ray crystal structure of 4a-ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol (1a), 3-bromo-4-(2,5-dimethoxyphenyl)-4-ethyl-1-methylpiperidine (7a•HBr), and 2-(3-bromo-4-ethyl-1-methylpiperidin-4-yl)benzene-1,4-diol (8a•HBr)

Single-crystal X-ray diffraction data on compounds **1a**, **7a•**HBr, and **8a•**HBr were collected using MoKα radiation and a Bruker APEX 2 CCD area detector. The structures was solved by direct methods and refined by full-matrix least squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C-H distance set at 0.96 Å. Atomic coordinates for these compounds have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 717736, 717737, and 717738 for compounds **1a**, **7a•**HBr, and **8a•**HBr respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk

4a-Ethyl-2-methyl-1,2,3,4,4a,9a-hexahydrobenzofuro[2,3-*c*]pyridin-6-ol (1a)

A 0.816 x 0.546 x 0.439 mm^3 crystal of **1a** was prepared for data collection coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was placed on a MicroMesh mount (MiTeGen, Ithaca, NY) and transferred immediately to the cold stream on the diffractometer. The crystal was triclinic in space group *P*-1 with unit cell dimensions *a* = 6.8808(3) Å, *b* = 8.7656(3) Å, *c* = 10.9505(5) Å, α= 100.844(2)°, β= 97.239(2)°, and γ = 106.358(2)°. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 91.8% complete to 25.0° θ (approximately 0.83 Å) with an average redundancy of 1.8.

3-Bromo-4-(2,5-dimethoxyphenyl)-4-ethyl-1-methylpiperidine (7a•HBr)

A 0.671 x 0.368 x 0.093 mm^3 crystal of **7a•**HBr was prepared for data collection coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was placed on a MicroMesh mount (MiTeGen, Ithaca, NY) and transferred immediately to the cold stream on the diffractometer. The crystal was monoclininc in space group $P2_1/n$ with unit cell dimensions *a* = 13.1119(4) Å, *b* = 7.4416(3) Å, *c* = 17.5915(8) Å, and β= 97.8690(10)°. Corrections were applied for

Lorentz, polarization, and absorption effects. Data were 99.4% complete to 28.35° θ (approximately 0.75 Å) with an average redundancy of 4.15.

2-(3-Bromo-4-ethyl-1-methylpiperidin-4-yl)benzene-1,4-diol (8a•HBr)

A 0.332 x 0.102 x 0.076 mm^3 crystal of **8a**•HBr was prepared for data collection coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was placed on a MicroMesh mount (MiTeGen, Ithaca, NY) and transferred immediately to the cold stream on the diffractometer. The crystal was monoclininc in space group $P\ 2_1 2_1 2_1$ with unit cell dimensions a = 7.3762(6) Å, b = 11.7948(9) Å, and c = 18.6205(13) Å. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 95.7% complete to 25.0° θ (approximately 0.83 Å) with an average redundancy of 2.77.

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