Probes for Narcotic Receptor Mediated Phenomena; 29: Synthesis of rac-(4R,6aR,11bR)-3-Methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]azocin-10-ol, the para-a Oxide-Bridged Phenylmorphan Isomer, and a New Route to rac-(4R,6aR,11bR)-3-Methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]azocin-8-ol, the ortho-a Oxide-Bridged Phenylmorphan Isomer

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Abstract: A six-step synthesis of the para-a oxide-bridged phenylmorphan isomer rac-(4R,6aR,11bR)-3-methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]azocin-10-ol (4), was achieved using Okahara’s reagent, 3-chloro-2-methoxyacetophene, to prepare the key intermediate 8. Bromination was directed at the desired carbon atom via the correctly positioned ketone moiety in 8. O-Demethylation followed by subsequent displacement of the bromine by the phenolic ion in situ gave ketone 9 that, after reduction to the alcohol and conversion to the bis-mesylate, could be reduced to obtain the desired product. The structure of 4 was unequivocally determined by an X-ray spectroscopic study. A similar sequence of reactions provided a novel, much shorter synthetic route to the known ortho-a oxide-bridged phenylmorphan isomer.

Key words: phenylmorphan, narcotic antagonist, drugs, ring closure, heterocycles

The 5-phenylmorphans are a particularly interesting class of µ-opioid receptor selective agonists that were initially prepared by May and Murphy in 1955, and are currently being reinvestigated. They have been transformed into ³-opioid receptor selective ligands, and, more recently, a considerable effort to convert 5-phenylmorphan agonists to pure ³-opioid antagonists succeeded with the synthesis of the (−)-N-phenylethyl analogue. To obtain selective and high affinity 5-phenylmorphan ³-opioid antagonists, the rotation of the aromatic ring may have to be fixed at an appropriate angle to the piperidine ring either via steric hindrance to rotation, or by some other mechanism, such as the synthesis of an oxide-bridged compound. The conformational requirement of the phenolic ring, that is, the angle between the plane of the aromatic ring and the piperidine ring that is needed to obtain phenylmorphan high affinity agonists or antagonists, is uncertain.

The original studies of May et al. revealed that a phenolic hydroxy group meta to the piperidine ring confers high opioid activity relative to the non-oxygenated analogue. In order to provide some further insight into the question of the 3-dimensional angular position of the phenolic ring, we have been involved in the synthesis of rigid analogues of oxide-bridged phenylmorphans. There are six oxide-bridged racemates possible (oxide-bridged at positions a–f, respectively, in Figure 1), with a phenolic hydroxy group ortho or para to the oxide bridge while retaining the required meta orientation to the piperidine ring (12 racemic compounds in all). The synthesis and pharmacological evaluation of these compounds, and their enantiomers bearing a ‘correct’ N-substituent, such as an N-phenylethyl group, would aid the determination of the specific angle between the phenolic and piperidine rings needed for a ligand to bind to an opioid receptor with high affinity as an agonist or antagonist. We have previously reported the synthesis of rac-(4R,6aR,11bR)-3-methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]azocin-8-ol (1), the ortho-a oxide-bridged phenylmorphan isomer, rac-(1R,4aR,9aR)-2-methyl-1,3,4,9a-tetrahydro-2H-1,4a-propanobenzofuro[2,3-c]pyridin-8-ol (2), the ortho-f oxide-bridged phenylmorphan isomer, and rac-(3R,6aS,11aR)-2-methyl-1,3,4,5,6,11a-hexahydro-2H-3,6a-methanobenzofuro[2,3-c]azocin-10-ol (3), the ortho-d oxide-bridged phenylmorphan isomer. We now present a complete report of the synthesis of rac-(4R,6aR,11bR)-3-methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]azocin-10-ol (4), the para-a oxide-bridged phenylmorphan isomer, as well as a novel and shorter synthesis of the ortho-a oxide-bridged phenylmorphan isomer (1).

Figure 1 Possible o- or p-substituted oxide-bridged racemic phenylmorphan isomers a–f.

The synthesis of 4 required 4-(2,5-dimethoxyphenyl)-1-methyl-1,2,3,6-tetrahydropyridine (6). Later studies revealed that a close analogue of 6 is extremely neurotoxic. Compound 6 was obtained by the method of Evans from the reaction of lithiated 1,4-dimethoxybenzene (5).
and 1-methyl-piperidin-4-one. The yield of 6 noted in the original procedure, using PPA, was improved using the acidic conditions noted in Scheme 1.

We envisioned ring closure to the desired methanobenzo-furo[3,2-d]azocine ring skeleton via an attack of a phenolic oxygen atom on the specific carbon atom C-6a (see numbering system in 4) in the cyclohexane ring of the key intermediate ketone 5-(2,5-dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1] nonan-7-one (8). The necessary cyclohexyl carbon atom was activated by bromination of the correctly positioned ketone moiety.

As we and, more recently, others have noted, Okahara’s reagent (3-chloro-2-methoxymethoxypropene), can act as a useful acetonylating agent in the synthesis of phenylmorphans. Our ‘one-pot’ synthetic strategy was to use the procedure of Evans et al. to generate an enamine anion from 6 with BuLi and subject the enol obtained from acid hydrolysis to an intramolecular Mannich reaction to obtain 8, as shown in Scheme 2.

Scheme 2 Synthetic strategy for preparation of 8, the key intermediate in synthesis of 4.

A small amount of a by-product, 1-[4-(2,5-dimethoxyphenyl)-1-methyl-1,2,5,6-tetrahydropyridin-2-y]propan-2-one (7), was presumably formed through initial reaction at the carbon α to the nitrogen atom, a less-favored pathway, but an available atom. The 2-azabicyclo[3.3.1] nonan-7-one (8) was brominated, with 1 equivalent of Br₂, at a carbon atom α to the ketone and the quaternary carbon atom. We did not attempt to determine the structure of the resulting bromo intermediate(s). Monobromination could occur at either C-6 or C-8, but probably occurs at both. Bromination at C-6 and direct SN₂ displacement by phenoxide ion would give the observed product 9. Similarly, bromination at C-8 followed by SN₂ displacement would give the same product. It is likely that the bromination proceeded in a manner similar to other well-studied oxide bridge closures (e.g., dihydrothebainone to 1-bromodihydrocodeinone).

The dimethoxy substituents in the aromatic ring were converted to a phenolic intermediate using BBr₃ and the proximal phenolic oxygen, under basic conditions, displaced bromine to form the desired rac-(4R,6aR,11bR)-3-
methyl-2,3,4,5,6,6a-hexahydro-6-oxo-1H-4,11b-methanobenzofuro[3,2-d]azocin-10-ol (9). Reduction of the ketone with K-selectride in THF gave the 6-hydroxy compound, 
\[\text{rac-(4R,6aR,11bR)-6-hydroxy-3-methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]azocin-10-ol (10)}\]. Mesylation of the 6-hydroxy and aromatic hydroxy group to give 11, followed by LiBEt4H reduction, gave the final product, the desired \(\text{para-a}\) compound, \[\text{rac-(4R,6aR,11bR)-3-methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]azocin-10-ol (4)}\), as shown in Scheme 1. The structure of \(4\)-HBr was unequivocally determined by single-crystal X-ray analysis. The angle described between the least-squares plane of the aromatic ring and the 4 co-planar atoms in the piperidine ring (N3–C4–C11b–C1, in Figure 3) was found to be 72.0°.

This synthetic route was used to reduce the number of steps needed to prepare the oxide-bridged ‘ortho-a’ phenylmorphan, \[\text{rac-(4R,6aR,11bR)-3-methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d] azocin-8-ol (1)}\]. In our earlier 10 step synthesis \(11\) to an \(\text{ortho-a}\) oxide-bridged phenylmorphan isomer, \(\text{ortho-a oxidobridged phenylmorphan isomer}\)

![Figure 3 Results of the X-ray structure analysis on 4-HBr drawn using the experimentally determined parameters with the displacement ellipsoids at 20% probability levels.](image)

Mps were determined using a Thomas–Hoover mp apparatus and are uncorrected. Proton NMR spectra were obtained on a Varian XL-300 instrument. Mass spectra (CI) were obtained on a Finnigan 1015D instrument. Electron-ionization mass spectra (EI-MS) were obtained using a VG-Micro Mass 7070F mass spectrometer. Gas chromatographic analysis was performed on a Hewlett-Packard 5880 instrument equipped with a 25 m SE-30 capillary column and a flame-ionization detector. Combustion analyses were obtained at Galbraith Laboratories, Inc., Knoxville, TN, or at Atlantic Microanalytical Laboratories, Atlanta, GA. Infrared spectra were obtained on a Beckman 4230 spectrophotometer. Thin-layer chromatography (TLC) were performed using 250 μm Analtech GHLF silica gel plates.

**Single-Crystal X-Ray Diffraction Analysis of rac-(4R,6aR,11bR)-3-Methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]azocin-10-ol Hydrobromide (4-HBr)**

\(\text{C}_{15}\text{H}_{20}\text{NO}_{2} \cdot \text{Br}^+\), F.W. = 326.23, (0.15 × 0.22 × 0.40 mm \(^{-1}\)), monoclinic, space group \(\text{P2}_1/a\), \(a = 11.557(2)\) \(b = 10.569(2)\), \(c = 12.225(3)\), \(\beta = 108.36(2)\), \(V = 1417.2(2)\), \(Z = 4\), \(\rho_{calc} = 1.53\) mg mm \(^{-3}\), \(\rho(CuK\alpha) = 1.54178\) Å, \(\mu = 3.94\) mm \(^{-1}\), \(F(000) = 672\), \(T = 293 K\), \(R_y = 0.054\) for 1545 reflections. Data were collected on an automated Bruker P4 diffractometer equipped with an incident beam monochromator. Corrections were applied for Lorentz, polarization, and absorption effects. The structure was solved and refined with the aid of the programs in the SHEXLPLUS system of programs.\(^{22}\) The full-matrix least-squares refinement on \(F^2\) included atomic coordinates and displacement ellipsoids for all non-H atoms. H atoms were included using a riding model \(\text{coordinate shifts of C applied to attached H atoms, C–H distances set to 0.96 to 0.93 Å, H angles idealized, } U_{eq}(C)\text{ were set to 1.2 to 1.3 } U_{eq}(C)\text{. Coordinates only were refined for the hydrogen on the ni-
trogen atom. The crystal exhibited non-merohedral twinning along the a-axis. For the refinement reflections having h = 3, 6, 9 and 12 were dropped from the data set and the h = 0 reflections were refined with a separate scale factor. Atomic coordinates for 4 HBr have been deposited with the Cambridge Crystallographic Data Base, 12 Union Road, Cambridge CB2 1EZ, UK (deposit it@ccdc.cam.ac.uk).

**Synthesis of the para-a Isoomer (4)**

5-(2,5-Dimethoxyphenyl)-2-methyl-2-azabicyclo[3.3.1]nonan-7-one (8)

To a stirred mixture of 4-(2,5-dimethoxyphenyl)-1-methyl-1,2,3,6-tetrahydropyridine-2,3-dione (26 g, 0.15 mmol) in THF (120 mL) was added, dropwise, BuLi (1.6 M in hexane) (160 mL, 0.256 mol) at –60 to –20 °C during 20 min, and then stirred at –20 to –10 °C for 45 min. 3-Chloro-2-methoxymethoxypropene has indicated that a similar 4-phenyltetrahydropyridine is an extremely potent neurotoxin – care should be taken in handling this material (Note: studies have suggested that a similar 4-phenyltetrahydropyridine is an extremely potent neurotoxin – care should be taken in handling this material)

The mother liquor was evaporated, and recrystallized from MeOH–CHCl₃, and evaporated in vacuo. This was treated with aq HCl (6 N; 30 mL). After refluxing for 1 h, the mixture was cooled in a dry ice–acetone bath and quenched with acetone (5 mL), then treated with aq NH₄OH, extracted with CHCl₃, and dried (Na₂SO₄). After removal of solvent, the residue was treated with HCl–MeOH, then recrystallized from MeOH–Et₂O to afford HCl.

The reaction mixture was quenched with sat. aq NaHCO₃, and extracted with CHCl₃. The CHCl₃ extracts were washed with H₂O, dried (Na₂SO₄), and evaporated in vacuo. The residue was purified by column chromatography (SiO₂; CHCl₃–MeOH, 25:1–10:1 v/v) to afford a pale brown solid, which was recrystallized from EtOAc to give racemic 4-(R)-6,10-Dimethanesulfonyloxy-3-methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]jazocin-10-ol (10).

rac-(4R,6aR,11bR)-6-Hydroxy-3-methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]jazocin-10-ol (11)

To a stirred mixture of the ketone 9 (308 mg, 1.19 mmol) in THF (5 mL) was added dropwise K-Selectride (1 M in THF) (6 mol, 6 mmol) under dry ice–acetone cooling, and then stirred overnight. The reaction mixture was quenched with HCl (6 N, 5 mL), and evaporated in vacuo. The residue was dissolved with H₂O, basified with NH₄OH, extracted with CHCl₃, and dried (Na₂SO₄). After removal of solvent, the residue was treated with HCl–MeOH, then recrystallized from MeOH–Et₂O to afford 10 HCl.

Yield: 270 mg (76%); pale yellow solid; mp > 190 °C (decomp.).

**CIMS (NH₃):** m/z = 290 (MH⁺).

**CIMS (NH₄OH):** m/z = 262 (MH⁺).

**rac-(4R,6aR,11bR)-6,10-Dimethanesulfonyloxy-3-methyl-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]jazocine (11)**

To a stirred mixture of 10 HCl (560 mg, 1.88 mmol) and Et₃N (3.06 g, 30 mmol) in CHCl₃ (25 mL) was added methanesulfonyl chloride (1.21 g, 10 mmol) at 5 °C. The reaction mixture was stirred at r.t. for 3 h. The reaction mixture was evaporated with sat. aq NaHCO₃, and collected with CHCl₃. The CHCl₃ extract was dried (Na₂SO₄), and evaporated in vacuo. The residue was purified by column chromatography (SiO₂; CHCl₃–MeOH, 10:1 v/v) to afford 11.

Yield: 598 mg (76%); pale yellow solid.

**CIMS (NH₄OH):** m/z = 418 (MH⁺), 322 (MH⁺–MSO₂).

**rac-(4R,6aR,11bR)-3-Methyl-6-oxo-2,3,4,5,6,6a-hexahydro-1H-4,11b-methanobenzofuro[3,2-d]jazocin-10-ol (9)**

To a stirred solution of 8 HCl (1.00 g, 3.08 mmol) in CHCl₃ (35 mL) in an ice-salt bath was added a solution of Br₂ (0.65 g, 4.06 mmol) in CHCl₃ (10 mL) during 5 min, and then stirred at –3 °C for 15 min. BBr₃ (35 mL, 37 mmol) was added slowly at –3 °C, then stirred at r.t. for 10 min. After removal of solvent, the residue was treated with cold aq NaOH (10%; 50 mL) under ice–H₂O cooling and N₂ atmosphere, then stirred at 0 °C for 1 h. Aq NaOH was added to the reaction mixture (pH 9) and the mixture was then extracted with CHCl₃. The CHCl₃ extracts were washed with H₂O, dried (Na₂SO₄), and evaporated in vacuo. The residue was purified by column chromatography (SiO₂; CHCl₃–MeOH–NH₄OH, 5:1:0.05 v/v) and converted into its
HCl salt, which was recrystallized from MeOH–Et₂O to afford 4 HCl.

Yield: 190 mg (47%); colorless scales; mp 282 °C (decomp.).

The base was also converted to 4 HBr (from i-PrOH–H₂O).

Colorless prisms; mp 304 °C (decomp.).

The HBr salt was basified, and converted to the 4 furamate (from i-PrOH–H₂O).

Colorless prisms; mp 250–251 °C (decomp.).

IR (KBr): 3250, 1605, 1490, 1460 cm⁻¹.

Colorless needles; mp 183–185 °C.

The base was also converted to 5-(2,3-dimethoxyphenyl)-1-methyl-1,2,3,6-tetrahydropyridine (14) to a stirred solution of 4-(2,3-dimethoxyphenyl)-1-methyl-1,2,3,6-tetrahydropyridine (13) (700 mg, 3 mmol) (Note: studies have indicated that a similar 4-phenyltetrahydropyridine is an extremely potent neurotoxin – care should be taken in handling this material) in THF (2 mL) was added BuLi (1.6 M soln in hexane) (3.0 mL, 4.8 mmol) at –78 °C to r.t. overnight. The reaction mixture was quenched with HCl (4 M). After stirring at r.t. for 4 h, the reaction mixture was evaporated in vacuo, and purified by column chromatography (SiO₂; CHCl₃–MeOH, 20:1 v/v) to afford 4. Yield: 220 mg (55%); pale yellow crystals; mp 115–116 °C.

IR (KBr): 1700 cm⁻¹.

HBr salt (in DMSO–HCl) (32.1 mg, 0.1 mmol) was added to aq NaHCO₃ (1 mL) and treated with ethereal CH₂N₂ [prepared from N-methyl-N-nitrosopiperidine (4.0 g) and KOH (4 g)]. Stirring at r.t. for 15 min, the mixture was stirred at 5 °C under an N₂ atmosphere for 5 min. The reaction mixture was treated with sat. aq NH₄Cl (pH 9), and then extracted with CHCl₃–MeOH (15:1 v/v) and the extract was dried (Na₂SO₄). After removal of solvent, the residue was purified by column chromatography (SiO₂; CHCl₃–MeOH, 15:1 v/v) to afford 15. Yield: 1.28 g, 49%; colorless solid; mp 198 °C.

IR (KBr): 3440, 1725 cm⁻¹.

Yield: 190 mg (47%); colorless scales; mp 282 °C (decomp.).

IR (KBr): 3250, 1605, 1490, 1460 cm⁻¹.

Para- and ortho-Azocin-6-one Isomer (16)

To a stirred solution of 4-(2,3-dimethoxyphenyl)-1-methyl-1,2,3,6-tetrahydropyridine (15) (700 mg, 3 mmol) (Note: studies have indicated that a similar 4-phenyltetrahydropyridine is an extremely potent neurotoxin – care should be taken in handling this material) in THF (2 mL) was added BuLi (1.6 M soln in hexane) (3.0 mL, 4.8 mmol) at –78 °C to r.t. overnight. The reaction mixture was quenched with HCl (4 M). After stirring at r.t. for 4 h, the reaction mixture was evaporated in vacuo, and purified by column chromatography (SiO₂; CHCl₃–MeOH, 50:3 v/v) to afford 16. Yield: 1.28 g, 49%; colorless scales; mp 115–116 °C.

Yield: 190 mg (47%); colorless scales; mp 282 °C (decomp.).

IR (KBr): 1730 cm⁻¹.

H NMR (CDCl₃): δ = 1.69 (dd, J = 13.1, 2.8 Hz, 1 H), 1.84 (dq, J = 13.0, 2.6 Hz, 1 H), 2.03 (m, 1 H), 2.35 (s, NMe, 3 H), 2.3–2.6 (m, 3 H), 2.66 (d, J = 17.3 Hz, 1 H), 2.93 (s, NMe, 3 H), 3.2–3.6 (m, 1 H), 3.48 (s, 1 H, H-1), 3.87 (s, 3 H, OMe), 4.78 (s, 1 H, H-6a), 6.69 (dd, J = 7.4, 1.1 Hz, 1 H), 7.67 (dd, J = 8.1, 1.0 Hz, 1 H), 8.67 (m, 1 H, H-10).

CIMS (NH₃): m/z = 274 (MH⁺).

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