Facile Synthesis of 11-Hydroxy-2-methoxyaporphine: A Potential Dopamine D₁ Receptor Ligand

Yu-Gui Si, John L. Neumeyer

Alcohol and Drug Abuse Research Center, McLean Hospital, Harvard Medical School, 115 Mill Street, Belmont, MA 02478, USA
Fax +1(617)8552519; E-mail: jneumeyer@mclean.harvard.edu

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Abstract: 11-Hydroxy-2-methoxyaporphine was synthesized from oripavine in three steps with an overall yield of 37.8%. The key step involved the palladium on carbon catalyzed reduction of 11-hydroxy-2-methoxy-10-O-[(trifluoromethyl)sulfonyl]aporphine using magnesium metal in methanol at room temperature in the presence of ammonium acetate.

Key words: aporphine, synthesis, rearrangement, reduction, deoxygenation

Naturally occurring and synthetic aporphine alkaloids are of interest for their biological activity, particularly for their dopaminergic activity. Novel 2-substituted (–)-(R)-apomorphine analogues have been prepared in several laboratories including ours (Figure 1). It was observed that substituents in the 2-position of aporphines modulate dopaminergic D₂ activity and selectivity. Dopamine receptor affinity studies showed that (–)-(R)-2-hydroxy-N-propylnoraporphine [(–)-(R)-2-HO-NPA] and (–)-(R)-2-methoxy-N-propylnoraporphine [(–)-(R)-2-MeO-NPA, 1c] were among the most potent and highly selective agonists for the D₂ receptor. The selectivity and binding affinity of apomorphine was also modified by the elimination of the 10-hydroxy group in apomorphine. These investigations led to (–)-(R)-11-hydroxy-N-propylnoraporphine [(–)-(R)-11-HO-NPa, 2] a compound displaying even higher affinity and selectivity for the D₂ receptor than apomorphine. Based on these findings, we investigated the synthesis of a compound with the combination of a 2-methoxy group and elimination of the 10-hydroxy group such as 3.

Initially we speculated that if we could prepare the corresponding rearrangement precursor 4, then the target compound 3 should be obtained by the rearrangement of 4 under acid conditions (Scheme 1). Compound 4 could be available starting from morphine through path ‘a’ or from oripavine through path ‘b’. Alternatively target compound 3 could be prepared by reduction of triflate 7 through path ‘c’, which could be obtained through the acid-catalyzed rearrangement of 6 starting from oripavine or thebaine.
3-Deoxymorphine (9) was prepared from morphine using our previously reported procedure. Oxidation of 9 with manganese dioxide gave the enone 5 in 80% yield (Scheme 2). However, several attempts to convert the enone 5 into the key intermediate 4 failed. These conditions included Me₂SO₄/t-BuO/NMP, Me₂SO₄/t-BuOK/THF, Me₂SO₄/t-BuOK/HMPA, and Me₂SO₄/t-BuOK/18-crown-6/HMPA. The conversion of the enone 5 into the enol ester 11 or oxidation of the enol methyl ether 12 to 4 also failed.

We then turned our attention to path b (Scheme 1). O-Tri- 

flation of oripavine (oripavine could also be prepared from thebaine using the procedure reported by Rice) with N-phenyltrifluoromethanesulfonimide yielded 6 (Scheme 3). We speculated that further reduction of tri- 

flate 6 would yield the rearrangement precursor 4. How- 

ever, classic reduction conditions [Pd(OAc)₂, Ph₃P, HCOOH, Et₃N, DMF] decomposed the starting material even at room temperature. Using other palladium sources [Pd(PPh₃)₄, Pd(PPh₃)₂Cl₂], phosphorus ligand (DPPP, DPPF), and base (Bu₃N) all led to decomposition.

The procedure reported recently by Sajiki using palladium on carbon and magnesium in the presence of ammonium acetate also failed in this reduction.

An alternative procedure to synthesize the target comp- 
ound 3 was thus attempted. Acid-catalyzed rearrange- 
ment of the triflate 6 gave the aporphine triflate 7 in 56% yield (Scheme 3). Palladium-catalyzed reduction of tri- 
flate 7 under previously reported standard conditions [Pd(OAc)₂, Ph₃P, HCOOH, Et₃N, DMF] furnished the catecholaporphine 10 in 56% yield but only 5% yield of desired compound 3. Using other palladium sources and phosphorus ligands led to similar results. Reduction of the 11-acetate derived from 7 also led to the catecholaporphine 10. Fortunately using palladium on carbon catalyzed with magnesium in the presence of ammonium acetate was successful in this reduction. After several at- 
tempts, it was found that 3 could be obtained in 75% iso- 
lated yield when 20% weight palladium on carbon, 3.0 equivalents magnesium, and 5.0 equivalents ammonium acetate were used in methanol at room temperature.

Scheme 2  Attempts to synthesize compound 4
played good affinity and selectivity at the D1 receptor. ammonium acetate. As expected, this compound dis-

In conclusion, 11-hydroxy-2-methoxyaporphine (44.28 g, 11 mmol) was added to the mixture of oripavine (2.97 g, 10 mmol) and Et3N (2.1 mL, 15 mmol) in CH2Cl2 (50 mL). The resulting mixture was stirred at r.t. for 3 h. The mixture was washed with H2O (30 mL) and brine (30 mL). The organic layer was dried (anhyd Na2SO4), and the solvent was evaporated. The residue was dissolved in Et2O (60 mL) and extracted with 1 M HCl (4 × 50 mL). The combined acidic layers were basified with NH4OH soln, and the mixture was extracted with CH2Cl2 (3 × 50 mL). The combined organic layers were washed with brine (80 mL) and dried (anhyd Na2SO4); the solvent was evaporated. The residue was purified by short column chromatography (silica gel, CH2Cl2–MeOH, 20:1) to yield 6 (3.9 g, 90%); mp 143–145 °C.

1H NMR (300 MHz, CDCl3): δ = 6.94 (d, J = 8.5 Hz, 1 H), 6.66 (d, J = 8.5 Hz, 1 H), 5.59 (d, J = 6.4 Hz, 1 H), 5.39 (s, 1 H), 5.06 (d, J = 6.4 Hz, 1 H), 3.64 (d, J = 6.9 Hz, 1 H), 3.61 (s, 3 H), 3.34 (d, J = 18.6 Hz, 1 H), 2.82–2.63 (m, 3 H), 2.46 (s, 3 H), 2.24 (ddd, J = 12.6, 5.1, 5.1 Hz, 1 H), 1.75 (dd, J = 12.6, 1.8 Hz, 1 H).

13C NMR (75 MHz, CDCl3): δ = 152.0, 147.85, 136.0, 135.7, 131.2, 131.1, 121.5, 119.7, 118.7 (q, J = 318 Hz), 112.2, 96.3, 90.8, 60.3, 55.0, 45.9, 45.7, 43.2, 36.6, 29.8.

11-Hydroxy-2-methoxy-10-0-[(trifluoromethyl)sulfonyl]aporphine (7) Triflate 6 (2.4 g, 5.6 mmol) was dissolved in 99% MeSO3H (15 mL, 232 mmol) under N2 at r.t. The resulting mixture was stirred for 30 min at 90 °C, and then cooled to r.t. Ice-water (50 mL) was added and the mixture was basified with NH4OH soln, extracted with CH2Cl2 (3 × 50 mL). The combined organic extracts were washed with brine (50 mL) and dried (anhyd Na2SO4); the solvent was evaporated. The residue was purified by short column chromatography (silica gel, CH2Cl2–MeOH, 50:1) and recrystallized (MeOH) to yield 7 (1.35 g, 56%) as a white solid; mp 168–170 °C.

1H NMR (300 MHz, DMSO-d6): δ = 7.66 (br, 1 H), 7.24 (d, J = 8.1 Hz, 1 H), 7.18 (d, J = 2.7 Hz, 1 H), 6.95 (d, J = 8.1 Hz, 1 H), 6.71 (dd, J = 12.9, 2.7 Hz, 1 H), 3.75 (s, 3 H), 3.25–2.67 (m, 6 H), 2.44 (s, 3 H), 2.38–2.16 (m, 1 H).


11-Hydroxy-2-methoxyaporphine (3) Under N2, Mg (36 mg, 1.5 mmol) and NH4OAc (193 mg, 2.5 mmol) were added to a mixture of triflate 7 (215 mg, 0.5 mmol) and 10% Pd/C (44 mg) in MeOH (15 mL) at r.t. The resulting mixture was stirred at r.t. for 24 h and filtered with Celite. The residue was washed with MeOH (2 × 20 mL). The filtrate was evaporated to dryness and dissolved in CH2Cl2 (100 mL). The soln was washed with 10% NH4OH (30 mL) and brine (50 mL). The organic layer was dried (anhyd Na2SO4) and evaporated in vacuo to dryness. The residue was purified by short column chromatography (silica gel,
CH₂Cl₂−MeOH, 100:1) and recrystallized (CH₂Cl₂) to yield 3 (105 mg, 75%) as a colorless solid; mp 215–216 °C.

\(^1\)H NMR (300 MHz, CDCl₃): \(\delta = 7.61 \ (d, J = 2.7 \ Hz, 1 \ H), \ 7.68 \ (d, J = 7.5 \ Hz, 1 \ H), \ 7.67 \ (d, J = 7.5 \ Hz, 1 \ H), \ 6.61 \ (d, J = 2.7 \ Hz, 1 \ H), \ 3.80 \ (s, 3 \ H), \ 3.25–3.02 \ (m, 4 \ H), \ 2.98 \ (m, 3 \ H), \ 2.55 \ (s, 3 \ H).

\(^1^C\) NMR (75 MHz, CDCl₃): \(\delta = 158.0, \ 152.8, \ 138.5, \ 134.5, \ 132.4, \ 128.2, \ 127.4, \ 120.7, \ 115.6, \ 111.9, \ 111.1, \ 61.8, \ 55.2, \ 53.1, \ 43.9, \ 35.3, \ 29.4.

\(^1^C\) NMR (75 MHz, CDCl₃): \(\delta = 159.4, \ 145.5, \ 144.4, \ 134.9, \ 132.2, \ 120.7, \ 115.6, \ 114.5, \ 114.0, \ 112.4, \ 63.7, \ 55.5, \ 54.1, \ 43.8, \ 35.5, \ 29.8.

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