Preparation of (*R*)-11-Hydroxyaporphine Directly from (*R*)-10,11-Dihydroxyaporphine ((*R*)-Apomorphine)

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A Regioselective synthesis of (*R*)-11-hydroxyaporphine **2** directly from (*R*)-10,11-dihydroxyaporphine ((*R*)-apomorphine, **1**) is described for the first time. The isopropylidene ketal ring of 10,11-(isopropylidenyldioxy)aporphine **5** obtained by the isopropylidenation of apomorphine was regioselectively opened by ten equivalents of trimethylaluminum to give (*R*)-10-hydroxy-11-*tert*-butyloxyaporphine **6**. The free 10-hydroxyl position of **6** was triflated with *N*-phenyltrifluoromethanesulfonimide and potassium carbonate under reflux to give (*R*)-10-[(trifluoromethyl)sulfonyloxy]-11-*tert*-butyloxyaporphine **7**. The reduced product, 11-*tert*-butyloxyaporphine **8** was prepared from **7** by a palladium-catalyzed hydrogenolysis. The ether cleavage of (*R*)-11-*tert*-butyloxyaporphine with 48% hydrobromic acid afforded the desired (*R*)-11-hydroxyaporphine **2** in good yield.

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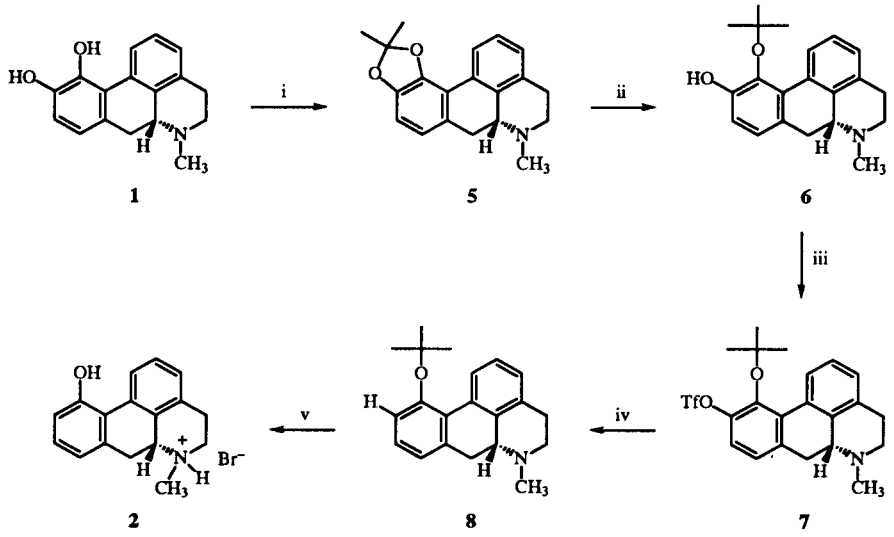
Small structural changes in aporphine derivatives may lead to drastic changes in pharmacological profiles. (*R*)-Apomorphine **1**, which was first synthesized around 1869 [1], acts as an agonist on central dopamine receptors [2]. In contrast, (*R*)-11-hydroxyaporphine **2** seems to be a dopamine receptor antagonist [3]. The monophenolic **2** has affinity for dopamine receptors but failed to display agonist activity in a serum prolactin assay indicating lack of agonist activity at dopamine receptors [3].

Replacement of the C-10-hydroxy group of **1** with a methyl group, providing (*R*)-10-methyl-11-hydroxyaporphine **3**, produced a potent 5-hydroxytryptamine receptor agonist which did not produce any dopaminergic effect in the cat cardiovascular nerve test [4]. These studies have shown that the catechol function of **1** is not a prerequisite for a potent interaction of aporphines with central dopamine receptors. (*R*)-11-Hydroxy-*N*-propylnoraporphine **4** has been reported by Neumeyer and coworkers [5] to be equipotent to **1** as a central dopamine receptor agonist. In more recent studies, however, compound **4** appears to be more potent than **1**, reportedly having higher affinity to and efficacy at dopamine receptors [6].



Reagents: (i) 2,2-dimethoxypropane, TsOH, dimethylformamide, N_2; (ii) 10 equivalents $Al(CH_3)_3$, CH_2Cl_2, -78°C/7 hours; rt/24 hours; (iii) $PhN(Tf)_2$, Et_3N-K_2CO_3, CH_2Cl_2, reflux; (iv) $(PPh_3)_2PdCl_2$, $Ph_2P(CH_2)_3PPh_2$, Bu_3N, HCOOH, dimethylformamide, 80°C; (v) 48% HBr, N_2, 130°C/25 minutes: Tf = CF_3SO_2.

Absolute configuration is also critically important for interaction at dopamine receptors. Only the *R*-(-) enantiomer of apomorphine, obtained by the acid-catalyzed rearrangement of the natural product (-)morphine, possesses dopamine agonist acvtivity. The structural requirements for activity at dopamine receptors of a variety of hydroxylated aporphines and structurally related dopamine agonists led to an hypothesis relating to the mode of binding of such agonists to dopamine receptors [7].

In order to understand the remarkable differences in pharmacological profiles in compounds **1-4**, we required a quantity of (*R*)-11-hydroxyaporphine **2**. Previously compound **2** has been prepared through the synthesis of the precursor, 1-(methoxy-2-nitrobenzyl)isoquinoline which was obtained from 2-nitro-3-methoxybenzoic acid and isoquinoline in a mutistep synthesis [8], followed by the so-called Reissert alkylation and Pschorr type cyclization procedures. The classical De Novo total synthesis requires at least more than ten synthetic steps [4]. Another strategy for the synthesis of monohydroxyaporphine **2** involved the removal of the phenolic hydroxyl group from morphine in several steps, followed by the acid-catalyzed rearrangement of natural morphine to apomorphine [9]. As described above, the conventional synthetic routes for this monohydroxylated aporphine **2** always entail multistep synthetic procedures or the acid-catalyzed rearrangement of natural morphine alkaloid to the corresponding aporphines.

In this respect, we wish to describe a simple and efficient synthesis of (*R*)-11-hydroxyaporphine **2** directly from the (*R*)-10,11-hydroxyaporphine (**1**, (*R*)-apomorphine). This simple synthetic procedure is the most practical one for converting apomorphine **1** directly to (*R*)-11-hydroxyaporphine **2**, and to the best of our knowledge, it is the first demonstration in the apomorphine series, since other methods failed to provide the direct (*R*)-hydroxyaporphine preparation.

Since X-ray analysis [10] had indicated that the phenolic 11-hydroxyl group of the biphenyl portion in the apomorphine system **1** is apparently strained due to its steric repulsion with the 1-*peri* hydrogen, we have developed a simple and practical regioselective method for the conversion of apomorphine **1** directly into (*R*)-11-hydroxyaporphine **2** in excellent yields. Due to the sterically hindered nature of the 11-hydroxyl position of the 10,11-(isopropylidenyldioxy)-aporphine molecule **5**, prepared readily from the isopropylidenation [11,12] of apomorphine, the bulky reagent, trimethylaluminum Lewis acid resulted in greater inaccessibility to the sterically hindered 11-ketal oxygen atom and controlled the association of the Lewis acid with the ketal oxygen [13] such that the bulky trimethylaluminum Lewis acid group coordinated regioselectively to the less hindered 10- ketal oxygen atom [14] only forming the (*R*)-10-hydroxy-11-*tert*-butyloxyaporphine **6** where the 10-hydroxyl group was intact. The free 10-hydroxyl group in compound **6** was then triflated [15] with *N*-phenyltrifluoromethanesulfonimide and potassium carbonate under reflux to give (*R*)-10-[(trifluoromethyl)sulfonyloxy]-11-*tert*-butyloxyaporphine **7**. The reduced product, 11-*tert*-butyloxyaporphine **8** was prepared from **7** by a palladium-catalyzed hydrogenolysis using the mixture of 1,3-bis(diphenylphosphino)propane, bis(triphenylphosphino)palladium dichloride, tributylamine and formic acid at 80° in dimethylformamide [16]. The ether cleavage of the (*R*)-11-*tert*-butyloxyaporphine molecule with 48% hydrobromic acid at the 130° for 25 minutes under a nitrogen atmosphere afforded the desired (*R*)-11-hydroxyaporphine **2** in good yield.

In conclusion, this simple synthetic procedure is the most practical one for converting apomorphine directly into (*R*)-11-hydroxyaporphine **2** and, to the best of our knowlege, it is the first demonstration in the apormorphine series, since other various methods failed to effect the direct deoxygenation of apomorphine.

EXPERIMENTAL

Melting points were determined on an electrothermal capillary melting point apparatus and uncorrected. Thin-layer chromatography was performed on glass plates coated with silicone oxide (silica gel $60F_{254}$) and compounds were visualized using a ultraviolet lamp. Proton and ^{13}C nuclear magnetic resonance spectra were obtained with a Varian Gemini 200 MHz, Bruker AM 300 and DPS 200 (solution in dimethyl sulfoxide-d_6 with tetramethylsilane as internal standard). Mass spectra were measured with Kratos MS 25 RFA (70eV, E1). The organic solvents and chemicals were obtained from commercial products and purified by the appropriate methods before use.

(*R*)-10,11-(Isopropylidenyldioxy)aporphine **5**.

To a stirred solution of 3.43 g (12.79 mmoles) of apomorphine **1** and 4.0 ml (32.6 mmoles) of 2,2-dimethoxypropane in 50 ml of dry dimethylformamide was added 49 mg (0.284 mmoles) of *p*-toluenesulfonic acid in 15 ml of dry dimethylformamide under a nitrogen atmosphere, and the reaction mixture was stirred at room temperature for 10 hours, and then added to an Amberite IRA-410 (OH form) ion exchange resin to remove the *p*-toluenesulfonic acid. The resulting resin was removed by filtration and washed with methanol. The combined washings and filtrate were evaporated *in vacuo* to yield sirupy residues which were chromatographed on silica gel (methanol:chloroform: ammonium hydroxide = 1:19:0.2) to yield 5.01 g (79%) of a light brown oil; ^1H-nmr (deuteriochloroform): δ = 1.33 & 1.59 (s, 6H, $C(CH_3)_2$), 2.84 (s, 3H, $N\text{-}CH_3$), 3.35 (m, 7H, aliphatic-H), 7.40-7.72 (m, aromatic-2H, 3H, 8H, 9H), 8.23 (m, 1H, aromatic-1H).

Anal. Calcd. for $C_{20}H_{21}NO_2$: C, 78.16; H, 6.89; N, 4.54. Found: C, 78.19; H, 6.97; N, 4.31.

(*R*)-10-Hydroxy-11-*tert*-butyloxyaporphine **6**.

A solution of 3.52 g (11.45 mmoles) of 10,11-isopropylidenyldioxy aporphine **5** in 50 ml of freshly distilled, dry methylene chloride was introduced under a nitrogen atmosphere to a flame dried round-bottomed flask, and cooled to -78°. Ten equivalents (2*M* solution in hexane) of trimethylaluminum was then added drop-

wise. The reaction mixture was stirred at -78° for 7 hours and at room temperature for 24 hours. It was then quenched by addition of aqueous ammonium chloride, and the precipitate was filtered. The filtrate was extracted with methylene chloride several times. The combined organic layers were washed with water, brine, and dried over anhydrous magnesium sulfate, and concentrated *in vacuo*. The foamy residue was chromatographed on sillica gel (hexane:ethyl acetate = 8:2) to give 2.78 g (78%) of the product; ^{1}H-nmr (dimethyl-d_6 sulfoxide): δ = 1.16 (s, 9H, *t*-Bu), 2.85 (s, 3H, *N*-CH_3), 3.02-3.34 (m, 7H, aliphatic-H), 5.90 (broad, s, 1H, aromatic-OH, exchangeable with deuterium oxide), 7.35-7.67 (m, 4H, aromatic-2H, 3H, 8H, 9H), 8.25 (m, 1H, aromatic-1H).

Anal. Calcd. for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79; N, 4.33. Found: C, 77.90; H, 7.59; N, 4.02.

(*R*)-10-[(Trifluoromethyl)sulfonyl]oxy-11-*tert*-butyloxyaporphine **7**.

A mixture of 3.07 g (8.59 mmoles) of *N*-phenyltrifluoromethanesulfonimide and 1.01 g (7.29 mmoles) of potassium carbonate were added to a refluxing (20 minutes) slurry of 1.81 g (7.20 mmoles) of **6** and 3.06 ml (22.05 mmoles) of triethylamine in 90 ml of methylene chloride, kept under a nitrogen atmosphere. Additional portions of 0.36 g (1.00 mmole) and 0.30 g (0.83 mmole) of *N*-phenyltrifluoromethanesulfonimide were added after 20 and 45 hours. After 75 hours, the heating was interrupted, and the reaction mixture was extracted with 10% aqueous sodium bicarbonate several times. The organic layer was dried (potassium carbonate), filtered, and concentated *in vacuo*. The oily residue was chromatographed on silica gel (methanol:chloroform:ammonium hydroxide = 1:19:0.2) to yield 2.24 g (79%) of a pure oil.;^{1}H-nmr (deuteriochloroform): δ 1.06 (s, 9H, *t*-Bu) 2.51-2.63 (m, 2H), 2.56 (s, 3H), 2.77 (dd, 1H), 2.84 (s, 3H), 3.05 (ddd, 1H), 3.13-3.25 (m, 3H), 7.14 (app d, 1H), 7.13-7.16 (m, 4H), 7.79 (app d, 1H); ^{13}C nmr (deuteriochloroform): δ 29.1, 35.0, 44.1, 52.8, 61.5, 118.5 (q), 121.4, 126.0, 126.6, 128.1, 128.3, 128.7, 128.8, 129.3, 133.3, 135.2, 139.7, 146.4.

Anal. Calcd. for $C_{22}H_{24}FNO_4S$: C, 58.06; H, 5.31; N, 3.08. Found: C, 57.87; H, 5.03; N, 2.93.

(R)-11-*tert*-Butyloxyaporphine **8**.

A mixture of 0.20 g (0.52 mmole) of **7**, 0.033 g (0.08 mmole) of 1,3-(diphenylphosphino)propane, 0.023 g (0.032 mmole) of bis(triphenylphosphino)palladium dichloride, 0.50 ml (2.08 mmoles) of tributylamine, and 60 μ (1.02 mmoles) of formic acid in 5.0 ml of dry dimethyformamide was stirred at 80° for 16 hours. The volatile materials were evaporated *in vacuo*, and the residue was partitioned between methylene chloride and 10% aqueous sodium bicarbonate. The organic layer was dried (potassium carbonate), filtered, and concentrated. The residue was chromatographed on silica gel; (methanol: chloroform: ammonium hydroxide = 1:19:0.2) to give 0.072 g (65%) of oily residue; ^{1}H-nmr (deuteriochloroform): δ = 1.06 (s, 9H, *t*-Bu), 2.55 (ddd, 1H), 2.57 (s, 3H), 2.63-2.81 (m, 2H), 2.84 (s, 3H, *N*-CH_3), 3.07 (ddd, 1H), 3.14-3.26 (m, 3H), 7.08 (app d, 1H), 7.20-7.35 (m, 4H), 7.56 (app d, 1H), 7.72 (app d, 1H); ^{13}C nmr (deuteriochloroform): δ 29.1, 34.1, 43.8, 53.4, 62.0, 121.2, 123.7, 126.8, 127.3, 127.5, 128.0, 128.3, 133.4, 133.5, 133.8, 134.4, 135.3.

Anal. Calcd. for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 81.98; H, 8.37; N, 4.59.

(*R*)-11-Hydroxyaporphine **2**.

A solution of 2.5 g (5.20 mmoles) of (*R*)-11-*tert*-butyloxyaporphine **8** in 40 ml of 48% hydrobromic acid was heated under nitrogen atmosphere in an oil bath at 130° for 25 minutes. Removal of the volatile products under reduced pressure left a solid residue which was recrystallized from ethanol (charcoal treated) to give 0.98 g (66%) of **2** hydrobromide, mp 279-283°; ^{1}H nmr (perdeuteriomethanol): δ 2.88 (1H, app t, $J_{7\alpha,6a\beta}$ = $J_{7\alpha,7\beta}$ =14 Hz, H-7α), 3.08-3.18 (1H, m, H-4), 3.01 (3H, s, N-CH_3), 3.30-3.58 (3H, m, H-4, H-5, H-7β), 3.76-3.82 (1H, m, H-5), 4.35 (1H, dd, $J_{6a\beta,7\beta}$ = 3.2 Hz, H-6aβ), 6.86 (1H, app d, $J_{10,9}$ = 7.6 Hz, H-10), 6.87 (1H, app d, $J_{8,9}$ =7.9 Hz, H-8), 7.11 (1H, dd, H-9), 7.17 (1H, app d, $J_{2,3}$ =7.6 Hz, H-3), 7.35 (1H, dd, $J_{2,1}$ =7.9 Hz, H-2), 8.40 (1H, app d, H-1); ^{13}C nmr (deuteriochloroform): δ 53.5 (C-5), 63.6 (C-6), 117.3 (C-10), 120.8 (C-8), 121.2, 127.7, 128.3, 128.9, 129.2, 130.0, 130.3, 133.8, 135.4, 156.2 (C-11).

Anal. Calcd. for $C_{17}H_{18}BrNO$: C, 61.46; H, 5.46; N, 4.22. Found: C, 60.95; H, 5.29; N, 4.14.

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