Towards an Efficient Preparation of Hydromorphone

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Dedicated to Prof. Dr. Wolf-Dieter Rudorf on the occasion of his 70th birthday. Ad multos annos!

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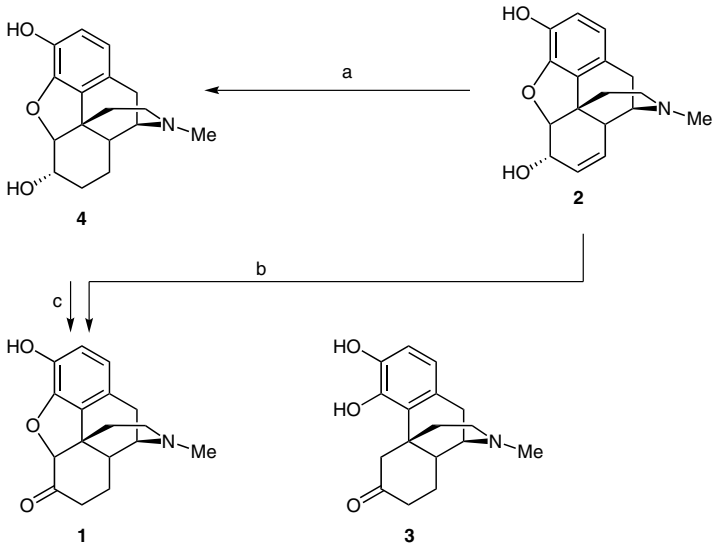
Abstract: Dihydromorphone was prepared from morphine in high yield, excellent purity, and low residual metal content. The key steps used palladium on porous glass and a modified Oppenauer oxidation, or Wilkinson's catalyst.

Key words: alkaloids, catalysis, oxidation, reduction, supported catalysis



Scheme 1 *Reagents and conditions:* (a) Pd on porous glass, H_2; (b) several Pt or Pd catalysts or Wilkinson's catalyst; (c) benzophenone, *t*-BuOH, toluene.

Opioid analgesics are among the most powerful pain relievers. They are used to treat chronic pain (e.g., due to cancer) or for the treatment of severe acute pain (e.g., following burns, surgery, or very serious injuries after an accident). Hydromorphone (**1**, Palladone®) is a potent centrally acting semi-synthetic opioid analgesic drug acting as a μ-opioid agonist.[1] This compound is able to cross the blood-brain barrier. Thus, it is used as an alternative to morphine (**2**) for analgesia and as a side-line narcotic antitussive. Its analgesic action is 3–4 times stronger than morphine, but it shows a lower dependence liability. It also causes less nausea than morphine. In 2010, in the USA 3445 kg of **1** were synthesized and available for medical use. During a project dealing with the synthesis of labeled **1**, we became interested in developing a synthetic scheme starting from morphine (**2**) yielding **1** in high yield and in high purity (Scheme 1).

Although **1** has been synthesized by many different routes,[2] among them the O-demethylation of codeine or analogues[3] or by microbial transformation[4] using strains of *Pseudomonas putida M10* or *Bacillus sp*., morphine (**2**) seems[2] the ideal starting material for the synthesis of **1**. Recently, isomerizations of **2** applying transition-metal catalysts[5–7] or noble metal catalysts[6,8] have been claimed in several patents.

Thus, treatment of **2** or its hydrochloride with catalytic or stoichiometric amounts of palladium or platinum under a variety of different conditions gave only low yields of **1**. The amount of **1** in the crude product never exceeded 40% as determined by HPLC. This finding is in excellent agreement with previous results.[9,10] Invariably under these conditions the accompanying formation of 3,4-dihydroxy-17-methylmorphinan-6-one (**3**) and dihydro compound **4** took place. Recently, palladium on porous glass

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has been suggested[11,12] as a superior catalyst system replacing traditional palladium on carbon catalysts. However, using palladium on porous glass, platinum on porous glass, palladium on graphite, or platinum on graphite[13] did not allow the exclusive formation of **1**. Although the isolation of pure **1** is possible by chromatography, the purification of crude **1** from these mixtures by recrystallization generally failed. Its purification via a bisulfite addition product,[14] however, worked nicely. Major drawbacks of these procedures are the low yields. We were not able to isolate pure **1** in more than 20–25% yield from these reactions. In addition, ICP-MS investigation of **1** obtained from these reactions showed the presence of 5–14 ppm of palladium or platinum (by leaching from the solid support).

In order to access multigram amounts of pure **1**, we set out to develop a robust, simple, and inexpensive synthesis. The reaction of **2** with Wilkinson's catalyst,[7] advanced smoothly, and **1** was obtained in 80% yield. No reaction, however, took place using **2**·HCl instead of the free base. Traces of hydrochloride reduced the yields. ICP-MS analysis of this material showed residual rhodium (7 ppm).

As an alternative we considered a two-step synthesis. Reduction of **2** using palladium on carbon (5 or 10%)[9] gave an excellent yield of **4**, however, because of leaching of the metal, residual palladium was found (>10 ppm). Reduction of **2** using palladium on porous glass proceeded nicely and gave an almost quantitative yield of dihydro **4** showing low residual palladium (<3 ppm).

Whereas oxidation of **4** using activated manganese dioxide, potassium permanganate, or platinum(IV) oxide/oxygen failed, an Oppenauer oxidation using modified Woodward/Rapoport conditions[9,15] yielded target compound **1** in 74% yield without the need for an extra recrystallization. The material obtained by this procedure showed a purity of >99.9% as established by HPLC.[16] ICP-MS analysis of this material showed residual palladium <0.1 ppm.

The reactions were monitored by TLC inspection on silica gel GF254 plates. The NMR spectra were recorded on a Varian Gemini 2000 (400 MHz). Mass spectra were obtained from a Finnigan Mat LLQ instrument. Melting points were measured on a Galen III instrument from Leica and are uncorrected. FT-IR were obtained using a Spectrum-1000 instrument, optical rotation using a polarimeter 341, and UV-vis using a Lambda 14 and for ICP-MS an Elan 9000 instrument (all from Perkin-Elmer). Experiments were conducted under BtM-permission no 4536217.

Dihydromorphine Hydrochloride (4)

The Pd on porous glass catalyst was prepared according to literature[11,17] from TRISOPOR porous glass and $Pd(OAc)_2$ yielding a catalyst with a loading of 1 wt% Pd.

A soln of morphine hydrochloride (10.0 g, 31.08 mmol) in 80% aq MeOH (300 mL) was hydrogenated in the presence of Pd on porous glass (1 g) at 25 °C at 4.14 bar for 2 h. The catalyst was filtered off, and the solvent was removed under diminished pressure to afford **4**·HCl (9.96 g, 99%) as a colorless solid; mp 287–290 °C (Lit.[18] 290 °C); $[\alpha]_D$ –109.6 (*c* 0.48, H_2O) {Lit.[19] $[\alpha]_D$ –112.0 (*c* 1, H_2O)}.

^1H and ^{13}C NMR spectra correspond to that in the literature.[18]

MS (ESI+): *m*/*z* = 288.4 $[M + H]^+$.

Hydromorphone (1) and Hydromorphone Hydrochloride (1·HCl)

From morphine (**2**): A soln of morphine (10.45 g, 36.62 mmol) in anhyd MeOH (105 mL) was heated under reflux for 5 min, and Wilkinson's catalyst (0.105 g) was added. The mixture was heated under reflux for 6 h, cooled to 0 °C for 2 h and filtered. The filter cake was washed with cold MeOH (5 °C, 4 × 25 mL each) and dried to yield **1** (6.7 g, 64%). The filtrate was evaporated, the remaining solids were dissolved in anhyd MeOH (5 mL), cooled to 0 °C for 1 h and filtered. This gave a 2nd crop of material (1.7 g); total yield of **1**: 8.4 g (80%). Compound **1** was obtained as a colorless solid; purity >99.8% by HPLC (see below); mp 264–266 °C (Lit.[2] 265–267 °C); $[\alpha]_D$ –192.9 (*c* 1, dioxane) {Lit.[9] $[\alpha]_D$ –194.0 (*c* 1, dioxane}; ICP-MS analysis of this material showed residual Rh 7 ppm.

From dihydromorphine hydrochloride (**4**): A mixture of **4**·HCl (9.3 g, 28.7 mmol), benzophenone (10.4 g, 57.4 mmol), and *t*-BuOK (17.7 g, 0.16 mol) in toluene (300 mL) was heated for 2 h at 85 °C. After cooling to 25 °C, 2 M aq HCl (100 mL) was added, the phases were separated, and the aqueous phase was extracted with Et_2O (100 mL) and pH was adjusted to 8.5 by addition of Na_2CO_3. After extraction with $CHCl_3$–*i*-PrOH (3:1, 2 × 200 mL), the organic phase is extracted with 10% HCl (3 × 50 mL), and the combined aqueous phases were concentrated under reduced pressure. The syrupy residue was triturated with MeOH (20 mL), the product began to crystallize, and crystallization was completed by standing at 5 °C for 2 h. The product was collected, washed with EtOH (10 mL) and Et_2O (20 mL), and dried to give **1**·HCl (6.8 g, 74%) as a colorless solid; purity >99.9% {HPLC [Lichrocart RP18, 22 °C, 4 × 250 mm, MeCN–H_2O, 35:65 + SDS (0.5% w/v) + AcOH (0.4% w/v), 1.0 mL/min, λ = 240 nm]: t_R = 23.5 min}; mp >280 °C (dec.) (Lit.[20] 280–295 °C); $[\alpha]_D$ –129.6 (*c* 0.50, H_2O) {Lit.[21] $[\alpha]_D$ –132.0 (*c* 2, H_2O)}. ICP-MS analysis of this material showed residual Pd <0.1 ppm.

^1H and ^{13}C NMR spectra correspond to that in the literature.[22]

MS (ESI+): *m*/*z* = 286.4 $[M + H]^+$, 570.9 $[2 M + H]^+$, 592.9 $[M + Na]^+$.

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