Transition metal-catalyzed redox isomerization of codeine and morphine in water

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**General Information:**

All transition metal-catalyzed reactions were carried out in sealed glass-vials under an atmosphere of nitrogen. Reagents were used as obtained from commercial suppliers without further purification.

Reactions in 100 g scale were carried out in a 1 L jacketed cylindrical reactor, diameter 100 mm; Manufacturer: G. Diehm (accessories: turbine stirrer, 70 mm diameter; immersed temperature pocket / baffle, 10 mm diameter).

$^1$H NMR spectra were recorded at 400 MHz; $^{13}$C NMR spectra were recorded at 100 MHz on a Bruker Advance spectrometer. $^1$H and $^{13}$C NMR chemical shifts (δ) are reported in ppm from tetramethylsilane using the residual solvent resonance (CHCl$_3$: δ$_H$ 7.26 and CDCl$_3$: δ$_C$ 77.2; or DMSO: δ$_H$ 2.50 and DMSO-δ$_6$: δ$_C$ 39.5). Coupling constants (J) are given in Hz.

Codeine (1) and morphine (2) were used as obtained from suppliers (Codeine base and Morphine CPS from Alcaliber S.A.) without further purification. [Rh(COD)(CH$_3$CN)$_2$]BF$_4$ (5) and 1,3,5-triaza-7-phosphaadamantane (L1, PTA, 97%) were purchased from Sigma-Aldrich and used without further purification. Deionized H$_2$O was degassed by bubbling N$_2$ for 30 min before it was used.

UPLC chromatograms were recorded on a Waters UPLC equipment with a gradient pump and a MS detector (TQD), column Waters Acquity BEH C18 (1.7 µm, 2.1 x 50 mm) using a solution 10 mM of ammonium formate in H$_2$O as mobile phase A and MeOH as mobile phase B (flow rate of 0.4 mL/ min and at 30 °C). The rate of the mobile phases was changed from 90% A : 10% B (0 min) to 10% A : 90% B (10 min).
Synthesis and characterization of hydrocodone (3):

Preparation of the catalyst: 1,3,5-Triaza-7-phosphaadamantane (L1) (5.4 mg, 0.033 mmol) and [RhCOD(CH$_3$CN)$_2$]BF$_4$ (5) (6.4 mg, 0.017 mmol) were stirred in deionized and degassed H$_2$O (10 mL) for some minutes prior to use until a clear solution was obtained.

Codeine base (1) (1.0 g, 3.34 mmol) was suspended in deionized and degassed H$_2$O (5 mL) and the suspension was heated to 100 °C. The catalyst solution (1.7 mM, 2 mL, 0.1 mol% Rh) was added and the reaction mixture was stirred vigorously at this temperature for 24 h. After cooling, the solid was filtered off and washed with H$_2$O (3 x 5 mL). The product 3 was dried under vacuum (< 2 mmHg) and obtained as an off-white solid (889 mg, 89%).

$^1$H NMR (400 MHz, CDCl$_3$, TMS): $\delta = 6.70$ (d, $J$(H,H) = 8.2 Hz, 1H), 6.63 (d, $J$(H,H) = 8.2 Hz, 1H), 4.65 (s, 1H), 3.91 (s, 3H), 3.18 (dd, $J$(H,H) = 5.4, 2.8 Hz, 1H), 3.02 (d, $J$(H,H) = 18.5 Hz, 1H), 2.62 – 2.51 (m, 2H), 2.43 (s, 3H), 2.42 – 2.26 (m, 3H), 2.19 (td, $J$(H,H) = 12.1, 3.5 Hz, 1H), 2.06 (td, $J$(H,H) = 12.1, 4.8 Hz, 1H), 1.89 – 1.77 (m, 2H), 1.26 (qd, $J$(H,H) = 13.2, 3.8 Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$, TMS): $\delta = 208.0$, 145.6, 143.0, 127.4, 126.5, 119.9, 114.8, 91.6, 59.4, 57.0, 47.1, 47.0, 43.1, 42.9, 40.4, 35.7, 25.7, 20.1.
Synthesis and characterization of hydromorphone (4):

Preparation of the catalyst: 1,3,5-Triaza-7-phosphaadamantane (L1) (7.9 mg, 0.049 mmol) and [Rh(COD)(CH3CN)2]BF4 (5) (9.3 mg, 0.025 mmol) were stirred in deionized and degassed H2O (7 mL) for some minutes prior to use until a clear solution was obtained.

The catalyst solution (2.5 mM, 7 mL, 0.7 mol% Rh) was added to morphine CPS (2) (1.0 g, 3.50 mmol) and the suspension was heated to 100 °C and stirred vigorously at this temperature for 24 h. After cooling to room temperature, the solid was filtered off and washed with H2O (3x5 mL). The product 4 was dried under vacuum (< 2 mmHg) and was obtained as white-grey solid (718 mg, 77%).

1H NMR (400 MHz, DMSO-d6, TMS): δ = 9.10 (s, 1H), 6.54 (d, J(H,H) = 8.0 Hz, 1H), 6.50 (d, J(H,H) = 8.1 Hz, 1H), 4.80 (s, 1H), 3.06 (dd, J(H,H) = 5.0, 2.7 Hz, 1H), 2.87 (d, J(H,H) = 18.3 Hz, 1H), 2.56 – 2.39 (m, 3H), 2.29 (s, 3H), 2.23 – 2.12 (m, 2H), 2.05 – 1.96 (m, 2H), 1.80 – 1.74 (m, 1H), 1.52 – 1.44 (m, 1H), 1.05 – 0.95 (m, 1H).

13C NMR (100 MHz, DMSO-d6, TMS): δ = 208.7, 144.0, 139.3, 127.4, 124.5, 119.2, 117.0, 90.4, 58.3, 46.4, 46.2, 42.5, 41.4, 39.7, 34.8, 25.0, 19.6.
Synthesis hydrocodone (3) in 100 g scale:

Preparation of the catalyst: 1,3,5-Triaza-7-phosphaadamantane (L1) (108 mg, 0.66 mmol) and [RhCOD(CH3CN)2]BF4 (5) (128 mg, 0.34 mmol) were dissolved in deionized and degassed H2O (20 mL) for some minutes prior to use until a clear solution was obtained.

Codeine (1) (100 g, 334 mmol) was suspended in deionized and degassed H2O (500 mL) in a 1 L jacketed cylindrical reactor, and the suspension was heated at 100 °C. The catalyst solution (20 mL, 0.1 mol% Rh) was added and the reaction was stirred vigorously at this temperature for 24 h. After cooling, the solid was filtered off and washed with H2O (3 x 100 mL). The solid was dried under vacuum (< 2 mmHg) to afford the title compound as off-white solid (90 g, 90%).
Hydrocodone (3)

$^1$H NMR (400 MHz, CDCl$_3$)
Hydrocodone (3)

$^{13}$C NMR (400 MHz, CDCl$_3$)
Hydromorphone (4)

$^{1}H$ NMR (400 MHz, DMSO-$d_6$)
Hydromorphone (4)

$^{13}$C NMR (400 MHz, DMSO-$d_6$)
Hydrocodone (3) (100 g scale)

$^1$H NMR (400 MHz, DMSO-$d_6$)
UPLC chromatogram of hydrocodone (3) (100 g scale, 0.1 mol% Rh)

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UPLC chromatogram of hydrocodone (3) (100 g scale, 0.15 mol% Rh)

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