Optimization of the Synthesis of Oxycodone and 5-Methyloxycodone

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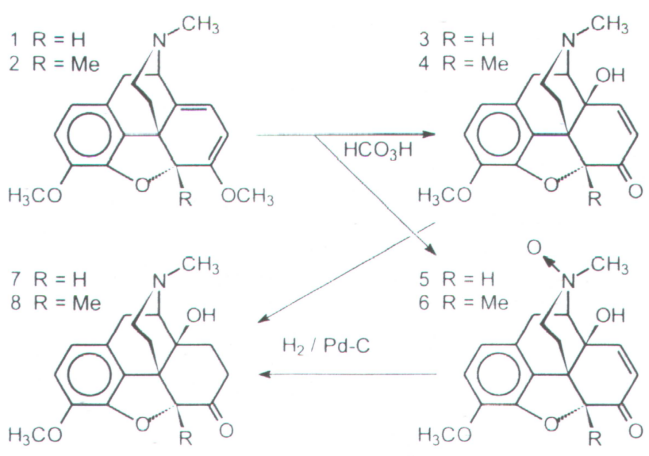
Oxidation of thebaine (**1**) to 14-hydroxycodeinone (**3**) as well as oxidation of 5-methylthebaine (**2**) to 14-hydroxy-5-methylcodeinone (**4**) afford the amine *N*-oxides **5** and **6**, respectively, as by-products. Therefore the process which usually follows (catalytic hydrogenation of the purified main-products **3** and **4**, respectively) leads to lower yields of the target compounds oxycodone (**7**) and 5-methyloxycodone (**8**) than hydrogenation of the respective mixture of oxidation products.

Formation of 14-hydroxycodeinone (**3**) and 14-hydroxy-5-methylcodeinone (**4**) from thebaine (**1**)[1,2] and 5-methylthebaine (**2**)[3,4], respectively, using performic acid always affords also a relatively hydrophilic by-product (detected by TLC). We decided to isolate it by column chromatography and to elucidate its structure. This by-product has been identified by MS (FAB) and NMR (^{1}H, ^{13}C, DEPT) as the amine *N*-oxide **5**[5] and **6**, respectively. Since **3** is often transformed by catalytic hydrogenation to the analgetically more potent dihydro-compound oxycodone (**7**)[1] which is not only used as analgesic, but also as starting material for the synthesis of the opioid antagonists naloxone and naltrexone, it seemed an obvious step to perform the reductive back-formation of the amine *N*-oxide to the amine simultaneously with this reaction step (the hydrogenation of **4** to 5-methyloxycodone (**8**)[4] is of less commercial importance although the 5-methyl compounds are pharmacologically more potent than the corresponding 5-H compounds). Using this process (without the purification of **3** and **4**) the overall yield of **7** and **8** was increased by ca. 10%.



Scheme

Experimental

Melting points (uncorrected): Kofler melting point microscope.– IR: Mattson FTIR 3000.– NMR: Varian Gemini-200.– MS (FAB): Varian MAT 95 (Institute for Organic Chemistry, University of Innsbruck).– Elemental analyses: Institute for Physical Chemistry, University of Vienna.– Chromatography: Mobile phase: CH_2Cl_2/MeOH/conc. NH_4OH (90:9:1). Stationary phase: TLC: Polygram SIL G/UV_{254} (Macherey-Nagel). CC: Silica gel 0.040-0.063 (230–400 mesh).

Oxidation of Thebaine (**1**)

A solution of thebaine (5.00 g) in a mixture of 0.7% H_2SO_4 (7.0 ml), 88% HCOOH (2.2 ml) and 30% H_2O_2 (2.2 ml) was stirred at 35–40 °C for 20 h (TLC showed that in addition to a small quantity of by-product, traces of educt were still present). After the solution had been poured on ice and rendered alkaline with conc. NH_4OH, it was extracted with CH_2Cl_2 (3 × 25 ml). The combined organic layers were washed with H_2O, dried over Na_2SO_4, and evaporated to give 4.36 g of unpurified, crystalline 14-hydroxycodeinone. Treatment of half the quantity (2.18 g) of the residue with 15 ml of a CH_2Cl_2-EtOH-mixture (1:1) afforded 1.88 g (including 0.52 g from the mother liquor) of pure 14-hydroxycodeinone (**3**) (1.88 g × 2 = 3.76 g (74.7%)).

Catalytic Hydrogenation of 14-Hydroxycodeinone (**3**) *to Oxycodone* (**7**)

A solution of pure 14-hydroxycodeinone (1.88 g) in glacial acetic acid (20 ml) was hydrogenated over 10% Pd-C-catalyst (200 mg) at 30 psi for 2.5 h. The catalyst was filtered off and the residue washed repeatedly with acetic acid. Then the filtrate was evaporated to give an oily residue which was rendered alkaline with conc. NH_4OH and extracted with CH_2Cl_2 (3 × 15 ml). The combined organic layers were washed with H_2O, dried over Na_2SO_4 and evaporated. Treatment of the crystalline residue (1.72 g) with EtOH (1.5 ml) yielded 1.51 g (incl. 23 mg from the mother liquor) of pure oxycodone (79.8%; overall 59.6 %).

Catalytic Hydrogenation of Unpurified 14-Hydroxycodeinone to Oxycodone

A solution of unpurified 14-hydroxycodeinone (2.18 g) in glacial acetic acid (20 ml) was hydrogenated over 10% Pd-C-catalyst (250 mg) at 30 psi for 2.5 h. The catalyst was filtered off and the residue washed repeatedly with acetic acid. Then the filtrate was evaporated, to give an oily residue which was rendered alkaline with conc. NH_4OH and extracted with CH_2Cl_2 (3 × 15 ml). The combined organic layers were washed with H_2O, dried over Na_2SO_4 and evaporated. Treatment of the crystalline residue (1.95 g) with EtOH (2 ml) afforded 1.74 g of pure oxycodone (1.74 g × 2 = 3.48 g (overall 68.7%)).

Oxidation of 5-Methylthebaine (**2**)

A solution of 5-methylthebaine (5.00 g) in an ice cooled mixture of 0.7% H_2SO_4 (7.0 ml), 88% HCOOH (2.2 ml), and H_2O_2 30% (5.0 ml) was left to stand at 4 °C (refrigerator) for a week (TLC showed that in addition to a small quantity of by-product, traces of educt were still present). After the solution had been poured on ice and rendered alkaline with conc. NH_4OH, it was extracted with CH_2Cl_2 (3 × 25 ml). The combined organic layers were washed with H_2O, dried over Na_2SO_4, and evaporated to give 4.46 g of unpurified, crystalline 14-hydroxy-5-methyl-codeinone. Treatment of half

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the quantity (2.23 g) of the residue with EtOH (2 ml) gave 1.32 g (incl. 0.38 g from the mother liquor) of pure 14-hydroxy-5-methylcodeinone (**4**) (1.32 g × 2 = 2.64 g (52.5 %)).

*Catalytic Hydrogenation of 14-Hydroxy-5-methylcodeinone (**4**) to 5-Methyloxycodone (**8**)*

A solution of 14-hydroxy-5-methylcodeinone (1.32 g) in EtOH (40 ml) was hydrogenated over 10% Pd-C-catalyst (150 mg) at 30 psi for 2.5 h. After filtration the catalyst was washed repeatedly with EtOH and the filtrate was evaporated to give a crystalline residue (1.31 g) which was treated with EtOH (1 ml) to afford 1.15 g (incl. 210 mg from the mother liquor) of pure 5-methyl-oxycodone (86.6 %; overall 45.4 %).

*Catalytic Hydrogenation of Unpurified 14-Hydroxy-5-methylcodeinone to 5-Methyloxycodone (**8**)*

A solution of unpurified 14-hydroxy-5-methylcodeinone (2.23 g) in EtOH (70 ml) was hydrogenated over 10% Pd-C-catalyst (250 mg) at 30 psi for 2.5 h. After filtration the catalyst was washed repeatedly with EtOH and the filtrate was evaporated to give a semicrystalline residue (2.18 g) which was treated with EtOH (2 ml), whereupon 1.41 g (195 mg from the mother liquor) of pure 5-methyloxycodone (1.41 g × 2 = 2.82 g (totally 55.7 %)) were isolated.

Isolation of the Amine N-Oxides

The amine *N*-oxides **5** and **6** were isolated by column chromatography from the respective mixture of oxidation products. After the elution of the main products **3** and **4**, respectively, and untransformed educt with a mixture of CH_2Cl_2, MeOH, and conc. NH_4OH (90:9:1) the stationary phase (silica gel) was extracted with methanol (it was not possible to elute the rather hydrophilic amine *N*-oxides). The following data refer to the respective mixture of oxidation products:

14-Hydroxycodeinone (**3**): 78 % Amine *N*-oxide (**5**): 7%
14-Hydroxy-5-methylcodeinone (**4**): 78 % Amine *N*-oxide (**6**): 8 %

Analytical Data

*14-Hydroxycodeinone 17-Oxide (**5**)*

Mp 239–242 °C (dec.) (ref.[5] 243 °C (dec.)).– IR (KBr): $\tilde{\nu}$ = 1682 cm^{-1} (C=O).– ^{1}H-NMR ([D$_6$]DMSO): δ = 3.25 (s, 3H, 17-CH_3), 3.72 (m, 1H, 9-H), 3.74 (s, 3H, OCH_3), 4.86 (s, 1H, 5-H), 5.94 (d, *J* = 10.0 Hz, 1H, olefinic H), 6.69 (d, *J* = 8.3 Hz, 1H, aromatic H), 6.81 (d, *J* = 8.3 Hz, 1H, aromatic H), 6.94 (d, *J* = 10.0 Hz, 1H, olefinic H).– ^{13}C-NMR {^{1}H} ([D$_6$]DMSO): δ = 56.3 (OCH_3), 59.0 (17-CH_3), 70.3 (C-14), 72.8 (C9), 86.6 (C-5), 130.6 (C-7), 150.1 (C-8), 194.1 (C-6).– MS (FAB): *m/z* 330 [$(M+1)^+$], 313 [M^+ – O], 312 [M^+ – OH].

*14-Hydroxy-5-methylcodeinone 17-Oxide (**6**)*

Mp 178 °C (dec.).– IR (KBr): $\tilde{\nu}$ = 1680 cm^{-1} (C=O).– ^{1}H-NMR ([D$_6$]DMSO): δ = 1.59 (s, 3H, 5-CH_3), 3.24 (s, 3H, 17-CH_3), 3.69 (m, 1H, 9-H), 3.72 (s, 3H, OCH_3), 5.89 (d, *J* = 10.0 Hz, 1H, olefinic H), 6.66 (d, *J* = 8.3 Hz, 1H, aromatic H), 6.78 (d, *J* = 8.3 Hz, 1H, aromatic H), 6.89 (d, *J* = 10.0 Hz, 1H, olefinic H).– ^{13}C-NMR {^{1}H} ([D$_6$]DMSO): δ = 17.3 (5-CH_3), 56.4 (OCH_3), 59.1 (17-CH_3), 70.9 (C-14), 73.1 (C-9), 92.1 (C-5), 129.8 (C-7), 148.8 (C-8), 197.6 (C-6).– MS (FAB): *m/z* 344 [$(M+1)^+$], 327 [M^+ – O], 326 [M^+ – OH].– Anal. ($C_{19}H_{21}NO_5 \cdot 1.8\ H_2O$) C, H, N: calcd. C 60.73 H 6.60 N 3.73, found C 60.61 H 6.15 N 4.15.

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