Synthesis and Stereochemistry of the (9*S*,13*S*,14*S*)-3-Hydroxy-17-methylmorphinan-10-ols

Erno Mohacsi* and Jay P. O'Brien

Chemistry Research Department, Hoffmann-La Roche Inc.,
Nutley, New Jersey 07110

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O-Demethylation of (9*S*,13*S*,14*S*)-3-methoxy-17-methylmorphinan-10-one (**2**) to (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan-10-one (**3**) and reduction of **3** to 10α- and 10β-hydroxylated morphinans **4** and **5**, are described. The stereochemistry of these epimeric alcohols was established on the bases of ^{1}H nmr data.

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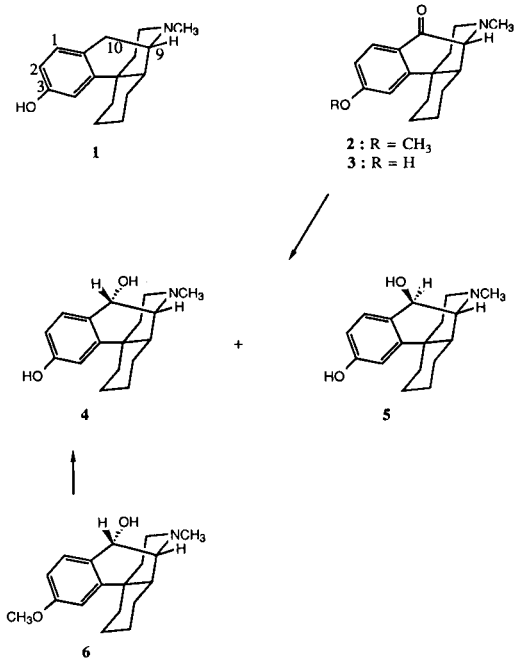
Dextrorphan, (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan (**1**) [1] is a potent anticonvulsant and neuroprotecting agent which acts in the central nervous system by blocking the *N*-methyl-D-aspartate subtype of glutamic acid receptor [2]. Our interest in the metabolic fate of **1** lead us to the preparation of the title compounds **4** and **5** since these morphinans could be metabolites of dextrorphan (**1**). In this paper we report the preparation of these epimeric alcohols as outlined in the Scheme.

Scheme



The starting material, (9*S*,13*S*,14*S*)-3-methoxy-17-methylmorphinan-10-one (**2**) was prepared according to the literature procedure [3]. *O*-Demethylation [4] of **2** with 48% aqueous hydrobromic acid at reflux temperature gave the desired (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan-10-one (**3**). The infrared spectrum of **3** (potassium bromide) showed a sharp absorption at 1671 cm^{-1}, which was assigned to the carbonyl group conjugated with the aromatic ring. In the uv spectrum of **3**, the absorption at 292 mμ reflected the influence of the carbonyl on the hydroxyphenyl chromophore. The ^{1}H nmr spectrum (deuteriochloroform) was in complete agreement with structure **3**. In particular, the signal of one low-field aromatic proton was at δ 8.01 indicating it was *ortho* to the carbonyl group. Lithium aluminum hydride reduction of **3** in refluxing tetrahydrofuran (THF) gave a 2.7:1.0 ratio of epimeric alcohols as determined by the intensity of the methine proton signal of the -C*H*(OH) group in the ^{1}H nmr spectrum. The major isomer (mp 236-238°) was separated from the mixture by fractional crystallization, while the minor isomer was separated from the concentrated mother liquors as a crystalline solid and obtained in pure form by recrystallization (mp 200-201°). Tentatively, structures **4** (mp 236-238°) and **5** (mp 200-201°) were assigned to these isomers, respectively. Conclusive evidence in support of the structural assignments came from spectral data. The mass spectrum of **4** showed the molecular ion peak as required at m/e 273 and the uv spectrum had two maxima at 229 and 280 mμ. The ir spectrum was devoid of carbonyl absorption but had hydroxyl absorption at 3260 cm^{-1}. Isomer **5** had similar ir, uv and ms spectra (see experimental part). The ^{1}H nmr spectrum of **4** features in particular a one-proton doublet at δ 4.58 (J = 7.5 Hz) for the methine proton at C-10, whereas the signal of the C-9 proton appeared as a doublet of doublets at δ 2.74 (J = 5 and 7 Hz). In comparison, the ^{1}H nmr spectrum of **5** showed a one-proton singlet at δ 4.68 for the methine proton at C-10 and the signal of the C-9 proton appeared as a doublet at 2.86 (J = 3 Hz). The stereochemistry at C-10 as indicated in structures **4** and **5** was assigned on the basis of ^{1}H nmr analysis. The Karplus equation [5] suggests that the coupling constant between vicinal protons is a function of the dihedral angle and reaches a maxima at 0 and 180° and a minimum at 90°. In the α-substituted morphinan **4** the dihedral angle between the 10β-proton ($H_{10\beta}$) and the vicinal proton (H_9) is about 30°, whereas in the 10β-substituted morphinan **5** the dihedral angle between the 10α-proton ($H_{10\alpha}$) and the vicinal proton (H_9) is about 90°. Therefore, $J_{H_{10\beta}H_9}$ would be expected to be larger than $J_{H_{10\alpha}H_9}$. The observed coupling constant for **4** and **5** was

$J_{H_{10\beta}\text{-}H_9}$ = 7.5 Hz and $J_{H_{10\alpha}\text{-}H_9}$ = 0, respectively, in agreement with the Karplus equation [5]. Thus, the major isomer (mp 236-238°) and the minor isomer (mp 200-201°) were assigned the structures and stereochemistry shown in formulas **4** and **5**, respectively. The relative configurational assignments were consistent with the reported stereochemistry of lithium aluminum hydride reduction of cyclic ketones [6]. If epimer formation is considered from the likely steric course of hydride delivery to **3**, attack from the least hindered face of the carbonyl group (steric control of asymmetric reduction [8]), giving the 10α-hydroxylated morphinan **4** is favored. Moreover, *O*-demethylation of the reported [3] (9*S*,13*S*,14*S*)-3-methoxy-17-methylmorpinan-10α-ol (**6**) with boron tribromide in methylene chloride yielded the 10α-alcohol **4**, indentical in all respects (mp, mmp and ^{1}H nmr) with a sample of **4** obtained by lithium aluminum hydride reduction of **3**. This experiment also supports the correctness of our previous structural assignments based on ^{1}H nmr data of the alcohols **4** and **5**.

Finally, the catalytic reduction of **3** with Raney nickel in ethanol and separation of the products by chromatography yielded the 10β-hydroxylated morphinan **5** along with some unreacted starting ketone **3** and a by-product in a ratio of about 1:1:0.5. The physical and chemical properties (mp, ir, uv and ^{1}H nmr) of the isolated 10β-alcohol **5** were identical with those of **5** prepared by lithium aluminum hydride reduction of **3**. The minor by-product was found to be identical (mp, mmp and ^{1}H nmr) with an authentic sample of dextrorphan (**1**) [1] and formed presumably from the benzylic alcohol **5** by hydrogenolysis. It should be mentioned that in the crude reaction mixture the presence of the epimeric 10α-hydroxylated morphinan **4** could not be detected by ^{1}H nmr spectroscopy.

EXPERIMENTAL

Melting points were taken in capillary tubes with a Thomas Hoover melting point apparatus and are uncorrected. Ultraviolet spectra were measured in 95% ethanol with a Carey Model 14 spectrophotometer. Infrared spectra were determined with a Beckman Model IR-9 spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian XL-400 spectrometer and recorded in δ values in deuteriochloroform or dimethyl sulfoxide-d_6/deuteriochloroform as the solvents and tetramethylsilane as an internal reference. The proton signals are designated as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Mass spectra (70 ev, direct inlet system) were determined with a CEC type 21-110 spectrometer.

(9*S*,13*S*,14*S*)-3-Hydroxy-17-methylmorphinan-10-one (**3**).

A mixture of 5.4 g (0.019 mole) of (9*S*,13*S*,14*S*)-3-methoxy-17-methylmorphinan-10-one (**2**) and 50 ml of hydrobromic acid (48%, aqueous) was heated at reflux for one hour and cooled to room temperature. The aqueous solution was made basic with concentrated ammonium hydroxide and extracted with chloroform (3 x 50 ml). The combined chloroform solutions were dried (magnesium sulfate) and removal of the solvent gave the crude product which after crystallization from acetonitrile afforded 3.9 g (76%) of (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan-10-one (**3**) as a white solid, mp 247-249°, $[\alpha]_D^{25}$ -100.0° (c 0.54, methanol); ir (potassium bromide): 1671 (ketone) cm^{-1}; uv (ethanol): λ max 231 mμ (ε 10150), 292 (13600) and 351 (398); ^{1}H nmr (deuteriochloroform): δ 8.01 (d, 1H, J_{ortho} = 7.2 Hz, ArH), 6.76 (m, 1H, ArH), 6.75 (s, 1H, ArH), 3.02 (t, 1H, J = 2.0 Hz, CHN), 2.37, (s, 3H, NCH_3), 2.12, 2.64 (m, 2H, NCH_2), 2.08 (m, 1H, CH_2CH) and 1.14-2.35 (10H, $5CH_2$); ms: (70 eV) m/e 271 (M^+).

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.79; N, 5.16. Found: C, 75.17; H, 7.78; N, 5.26.

The hydrochloride salt of **3** was prepared in ethyl acetate and recrystallized from ethanol/ether. The colorless crystals were isolated as the ethanolate, mp 108-110° (decomposition), $[\alpha]_D^{25}$ -5.96° (c 1.03, methanol); ir (potassium bromide): 1662 (ketone) cm^{-1}; uv (ethanol): λ max 204 mμ (ε 12850), 235 (8100) and 300 (12250).

Anal. Calcd. $C_{17}H_{21}NO_2 \cdot HCl \cdot CH_3CH_2OH$: C, 64.48; H, 7.97; H, 3.95. Found: C, 64.56; H, 7.70; N, 4.13.

(9*S*,13*S*,14*S*)-3-Hydroxy-17-methylmorphinan-10α- and 10β-ol **4** and **5**.

Under nitrogen, to a magnetically stirred slurry of 1.7 g of lithium aluminum hydride in 200 ml of dried tetrahydrofuran (dried over calcium hydride) was added portionwise 2.5 g (0.009 mole) of (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan-10-one (**3**). The mixture was heated at reflux for 12 hours and cooled to room temperature. The excess lithium aluminum hydride was decomposed by careful addition of ethyl acetate followed by a few drops of water. The slurry was filtered through a sintered glass funnel and the filtrate was concentrated under reduced pressure to afford 2.3 g of a mixture of crude alcohols **4** + **5** [7]. This mixture was recrystallized twice from ethanol to give 1.3 g (41%) of (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan-10α-ol (**4**) as a white solid, mp 236-238°, $[\alpha]_D^{25}$ +108.37° (c 0.98, 1*N* hydrochloric acid); ir (potassium bromide): 3260 (hydroxyl) cm^{-1}; uv (ethanol): λ max 229 mμ (ε 6750), 280 (1820) and 285 sh (1790); ^{1}H nmr (dimethyl sulfoxide-d_6/deuteriochloroform): δ 7.39 (d, 1H, J_{ortho} = 8.4 Hz, ArH), 6.75 (dd, 1H, J_{meta} = 2.5, J_{ortho} = 8.4 Hz, ArH), 6.66 (d, 1H, J_{meta} = 2.5 Hz, ArH), 4.58 (d, 1H, J = 7.5 Hz, HOC*H*), 2.74 (dd, 1H, J = 5 and 7 Hz, NCH), 2.63 (s, 3H, NCH_3) and 0.97-2.62 (13H, $6CH_2$, CH); ms: (70 eV) m/e 273 (M^+).

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.66; H, 8.49; N, 5.23.

The hydrochloride salt of **4** was prepared in ethyl acetate and recrystallized from ethanol to give the semihydrate as a white solid, mp 145° (sinters), $[\alpha]_D^{25}$ +6.94° (c 0.59, methanol); ir (potassium bromide): 3415 and 3330 (hydroxyl) cm^{-1}; uv (ethanol) λ max 229 mμ (ε 6780), 279 (1640) and 285 sh (1540).

Anal. Calcd. for $C_{17}H_{23}NO_2 \cdot HCl \cdot 0.5H_2O$: C, 64.04; H, 7.90; N, 4.39. Found: C, 64.34; H, 7.98; N, 4.48.

The combined mother liquors of **4** were concentrated under reduced pressure and the residue was recrystallized three times from acetone to give 0.398 g (16%) of (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan-10β-ol (**5**), mp 200-201°, $[\alpha]_D^{25}$ +65.17° (c 0.49, methanol); ir (potassium bromide): 3390 (hydroxyl) cm^{-1}; uv (ethanol): λ max 277 mμ (ε 1560) and 279 (1465); ^{1}H nmr (dimethyl sulfoxide-d_6/deuteriochloroform): δ 8.75 (br, 1H, OH), 7.33 (m, 1H, ArH), 6.74 (m, 2H, ArH), 4.68 (s, 1H, HOC*H*), 3.33 (br, 1H,

OH), 2.86 (d, 1H, J = 3 Hz, NCH), 2.48 (s, 3H, NCH_3) and 1.28-2.47 (13H, $6CH_2$, CH); ms: (70 eV) m/e 273 (M^+).

Anal. Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H 8.48; N, 5.12. Found: C, 74.62; H, 8.82; N, 5.02.

The maleate salt of **5** was prepared in acetone, mp 92-93°, $[\alpha]_D^{25}$ -62.18° (c 0.52 methanol); ir (potassium bromide): 3290 (hydroxyl) cm^{-1}; uv (ethanol): λ max 201 mμ (ε 52650), 277 (1840) and 284 sh (1680).

Anal. Calcd. for $C_{17}H_{23}NO_2 \cdot C_4H_4O_4$: C, 64.77; H, 6.99; N, 3.60. Found: C, 64.33; H, 7.28; N, 3.29.

O-Demethylation of (9*S*,13*S*,14*S*)-3-Methoxy-17-methylmorphinan-10α-ol (**6**).

To a slurry of 0.56 g (0.0017 mole) of (9*S*,13*S*,14*S*)-3-methoxy-17-methylmorphinan-10α-ol hydrochloride (**6**) in 20 ml of methylene chloride was added dropwise a solution of 2.5 ml (0.0025 mole) of boron tribromide (1.0*M* in methylene chloride) at ice-bath temperature. After the addition was completed, the mixture was stirred at room temperature for 17 hours and concentrated to dryness. The residue was partitioned between methylene chloride and dilute ammonium hydroxide. The methylene chloride solution was washed with water, dried (magnesium sulfate) and the solvent was removed under reduced pressure. The residue was crystallized from ethanol to give 0.36 g (75%) of (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan-10α-ol (**4**) as a white solid, mp 236-238°, identical in mp, mixed mp and ^1H nmr spectroscopy with **4** obtained by lithium aluminum hydride reduction of **3**.

Catalytic Reduction of (9*S*,13*S*,14*S*)-3-Hydroxy-17-methylmorphinan-10-one (**3**).

A solution of 2.0 g, (0.0074 mole) of (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan-10-one (**3**) in 200 ml of absolute ethanol was hydrogenanted using 1.0 g of Raney nickel at 70-80° and 50 psi for 24 hours. The catalyst was removed by filtration and the solvent was evaporated at reduced pressure to give a residue which was chromatographed using 40 g of silica gel. The column was eluted with 20 ml portions of a mixture of acetone--methanol (80:20 v/v). Fractions 1-9 after removal of the solvents gave 0.5 g (25%) of (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan-10-one (**3**) as a white solid, mp 247-249°, melted undepressed on admixture with the starting ketone **3**. Elution of the column was continued with the same solvent, fractions 13-24 yielded after removal of the solvent and recrystallization of the residue from ethyl acetate 0.5 g (25%) of (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan-10β-ol (**5**) as a white solid, mp 198-200°, identical in mp, mixed mp, thin layer chromatography (a mixture of chloroform/methanol/-ammonium hydroxide, 90:10: 0.4 v/v) and ^1H nmr spectroscopy with **5** obtained by lithium aluminum hydride reduction of **3**. Further elution of the column with the same solvent, fractions 28-42 yielded after removal of the solvent and recrystallization of the residue from benzene 0.3 g (16%) of (9*S*,13*S*,14*S*)-3-hydroxy-17-methylmorphinan (**1**) as a white solid, mp 197-199°, identical in mp [reported [1] mp 198-199°], mixed mp and ^1H nmr spectroscopy with an authentic sample of **1** [1].

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