Synthesis of (-)-1-Hydroxy-*N*-methylmorphinan-6-one and Its *O*-Methyl Ether from (-)-4-Hydroxy-*N*-formylmorphinan-6-one

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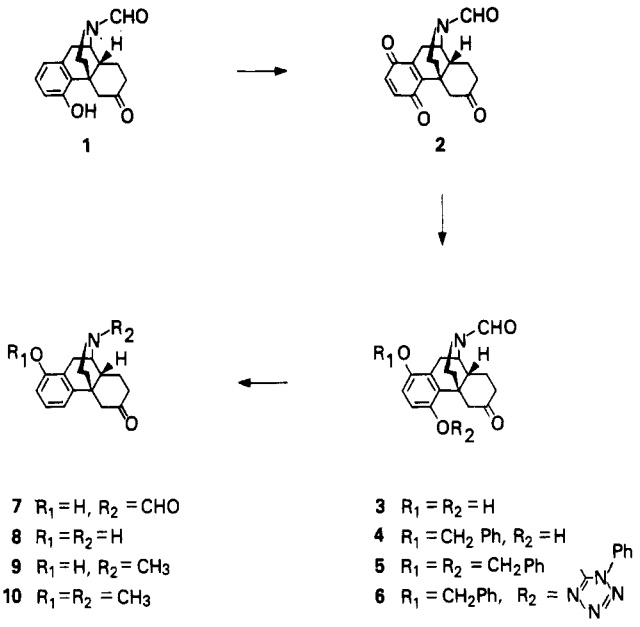
The *N*-formyl-protected 4-hydroxymorphinan-6-one (1) of the natural series afforded the hydroquinone 3 after oxidation with Fremy's salt and reduction of the *p*-quinone 2 with Zn in methanol in the presence of ammonium chloride. Protection of the 1-OH as benzyl- and the 4-OH as phenyltetrazolyl ether and reduction of the mixed diether over Pd/C in acetic acid gave the *N*-formyl-protected 1-hydroxymorphinan-6-one (7). Deprotection of 7 followed by N-methylation afforded the (-)-1-hydroxy-*N*-methylmorphinan-6-one (9) and, after O-methylation, the *O*-methyl ether 10. Both compounds, 9 and 10, were evaluated for their antinociceptive activity in the hot-plate assay in mice.

The 3- and 4-hydroxy-substituted *N*-methylmorphinan-6-ones of the natural series of opioids and their *O*-methyl ethers exhibit powerful antinociceptive properties,[1] whereas the 2-oxygenated analogues were found to be practically devoid of such qualities.[2] In order to discern whether an oxygen function at C-1 of 6-oxomorphinans would be equally detrimental to antinociception, we decided to prepare some representatives by a classical Grewe type synthesis, already utilized in the synthesis of (±)-1-hydroxy-*N*-methylmorphinan.[3,4]

Although the required isoquinoline precursor was readily obtained,[1] we failed to achieve a successful cyclization with acid. We now report on a successful conclusion of this task in chemically converting (-)-4-hydroxy-substituted morphinan-6-ones, prepared from natural morphine,[5-8] into the 1-oxygenated isomers. Oxidation of the *N*-formyl-protected oxomorphinan 1[6] with Fremy's salt,[9] a reaction explored by Beyerman et al. in the 3-hydroxy-substituted series of 6-oxomorphinans,[10] afforded the yellowish *p*-quinone 2. The spectral properties of 2 (MS, ^{1}H NMR, UV, and IR; see Experimental Section) were in agreement with its monomeric structure. Reduction of 2 with Zn/NH_4Cl in methanol afforded the hydroquinone 3. It is well-established that 3,4-dimethoxylated[11,12] and 2,4-dimethoxycarbonyloxylated morphinans[8] can selectively be cleaved at the sterically hindered 4-position to afford predominately the 4-hydroxy congeners. It was for this reason speculated that a partial O-alkylation of 3 would favor the O-alkylation at 1-OH, allowing later the elimination of the 4-OH. This assumption proved to be correct, since treatment of 3 with 1.1 mol of benzyl bromide in a mixture of $CHCl_3/CH_3OH$ in the presence of dry potassium carbonate afforded after chromatographic separation

Scheme I



7 R_1=H, R_2=CHO
8 R_1=R_2=H
9 R_1=H, R_2=CH_3
10 R_1=R_2=CH_3

3 R_1=R_2=H
4 R_1=CH_2Ph, R_2=H
5 R_1=R_2=CH_2Ph
6 R_1=CH_2Ph, R_2 =

the monobenzyl ether 4 besides the dibenyl ether 5 in a ratio of 5:1. The two ethers could readily be separated by column chromatography. The oily monoether 4 moved as the slower moving material and showed the expected spectral properties (MS, ^{1}H NMR). Treatment of 4 with 5-chloro-1-phenyl-1*H*-tetrazole in DMF in the presence of potassium carbonate at room temperature afforded the 1-benzyl-4-phenyltetrazolyl diether 6 as an amorphous material but secured in its structure by MS and ^{1}H NMR. Reduction of 6 over the twofold amount of 10% Pd/C in acetic acid at room temperature for 78 h gave after usual workup the 1-hydroxy-substituted oxomorphinan 7, which behaved on TLC as the usual pair of rotamers.

The conversion of 7 into the *N*-methyl congener 9 was accomplished by reaction sequences explored earlier in another series[6] and afforded the amine 8 as a crystalline norbase. Reductive N-methylation of 8 gave after usual workup the high-melting phenol 9. In other experiments chromatography on silica gel was used to purify the pinkish phenolic material. The oxomorphinan 9 can be differentiated from its three isomers investigated earlier by TLC; the following order of decreasing R_f values was found: 4-OH > 3-OH > 1-OH > 2-OH. The morphinan 9 is further characterized by its ^{1}H NMR spectrum, showing the signals for the three aromatic protons at δ 6.97 (dd, 1 H), 6.76 (d, 1 H), and 6.53 (d, 1 H). Further physical data are listed in the Experimental Section. O-

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Methylation of **9** with phenyltrimethylammonium chloride in DMF in the presence of potassium carbonate[2] afforded the crystalline *O*-methyl ether **10**. The phenol **9** did not show antinociception at 50 mg/kg when tested in the hot-plate assay in mice, whereas the *O*-methyl ether **10** had an ED_{50} of 3.7 mg/kg in this assay.[1]

Experimental Section

Melting points (uncorrected) were determined with a Fisher-Johns apparatus. Elemental analyses were performed by the Section on Microanalytical Services and Instrumentation of this laboratory. IR spectra were recorded on a Beckman IR 4230 spectrometer. Optical rotations were measured by using a Perkin-Elmer Model 241 MC polarimeter with the solvents and concentrations specified. NMR spectra were determined by using a Varian HR-220 spectrometer or a JEOL JNM-FX 100 spectrometer and reported in parts per million relative to Me_4Si as internal reference (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet; *J* (in hertz) = apparent coupling constant). Chemical-ionization (CI) mass spectra were obtained by using a Finnigan 1015 D spectrometer with a Model 6000 data collection system. Electron-ionization (EI) mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer (70 eV). Ultraviolet spectra were determined in 95% EtOH, using a HP 8450A UV/vis spectrophotometer. Thin-layer chromatography (TLC) utilized silica gel GF plates from Analtech, Inc.; solvent system for the amides was AcOEt and for the bases $CHCl_3$/MeOH/NH_4OH (90:9:1). For column chromatography alumina (Aldrich) or silica gel 60, 230–400 mesh ASTM, EM Reagent was used.

(−)-1,4-Dihydro-*N*-formylmorphinan-1,4,6-trione (2). Four hundred milliliters of an aqueous solution of NaH_2PO_4 (6.1 g, 50.83 mmol) and of Fremy's salt (10.4 g, 38.76 mmol) was added during a period of 20 min to a stirred solution of **1** (2.8 g, 9.81 mmol) in 250 mL of MeOH while a temperature of 10–15 °C was maintained. Three hundred milliliters of H_2O was added, and the solution was kept at room temperature for 1 h and then cooled again to 10–15 °C. Four hundred milliliters of an aqueous solution of NaH_2PO_4 (6.1 g, 50.83 mmol) and of Fremy's salt (10.4 g, 38.76 mmol) was added at once, and the mixture stirred for 1 h at room temperature and then extracted several times with a total volume of 300 mL of $CHCl_3$. The organic layer was dried and evaporated to yield a dark oil of **2** (2.85 g, 97%), which was used for the next step without further purification. For **2** (sample crystallized from MeOH): mp 200–202 °C dec; $[\alpha]^{25}_D$ −280.0° (*c* 0.56, DMF); MS (EI), *m/e* 299 (M^+); IR (KBr) 1705 (CO), 1670 (quinone), 1650 (NCHO) cm^{-1}; UV 215 nm (ε 9700); NMR ($CDCl_3$) δ 8.12 and 7.96 (s, 1 H, NCHO, pair of rotamers), 6.64 (s, 2 H, CH=CH), 4.84 (m, 1 H, C9-H).

Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.73; N, 4.68. Found: C, 68.15; H, 6.00; N, 4.58.

(−)-1,4-Dihydroxy-*N*-formylmorphinan-6-one (3). Activated zinc powder (6.0 g, 0.92 mol) was added in portions to a refluxing mixture of **2** (2.85 g, 9.53 mmol) and NH_4Cl (6.0 g, 0.11 mol) in 100 mL of MeOH, during a period of 5 min. After refluxing for an additional 5 min, the mixture was filtered and the filtrate concentrated in vacuo to ca. 50 mL. Fifty milliliters of H_2O was added, and the mixture was concentrated in vacuo again to ca. 50 mL. The precipitate was collected, washed with H_2O, and dried to yield **3** (2.35 g, 82%) as a pink solid. An analytical sample was prepared by recrystallization from MeOH: mp 297–302 °C dec; $[\alpha]^{25}_D$ −144.5° (*c* 0.47, DMF); MS (EI), *m/e* 301 (M^+); IR (KBr) 3380 (OH), 1695 (CO), 1645 (NCHO) cm^{-1}; NMR (Me_2SO-d_6) δ 8.80 (s, 1 H, OH), 8.68 (s, 1 H, OH), 8.14 and 7.98 (2 s, 1 H, NCHO, pair of rotamers), 6.48 (t, 2 H, Ar H, *J* = 8 Hz), 4.64 (m, 1 H, C9-H).

Anal. Calcd for $C_{17}H_{19}NO_4$·0.5MeOH: C, 66.23; H, 6.67; N, 4.41. Found: C, 66.52; H, 6.67; N, 4.68.

(−)-1-(Benzyloxy)-*N*-formyl-4-hydroxymorphinan-6-one (4) and (−)-1,4-Bis(benzyloxy)-*N*-formylmorphinan-6-one (5). A mixture of 100 mL of $CHCl_3$, 50 mL of MeOH, and anhydrous K_2CO_3 (5.0 g, 36.18 mmol) was refluxed for 15 min under a stream of argon. Then **3** (2.5 g, 8.30 mmol) and benzyl bromide (1.1 mL, 9.24 mmol) were added, and the mixture was refluxed for 4 h. After filtration, the filtrate was evaporated, and the residue was dissolved in $CHCl_3$, washed with 1 N HCl, dried, and evaporated to give 3.2 g of a brown oil. This residue was chromatographed on silica gel (CH_2Cl_2/MeOH = 40:1) to afford the dibenzyl ether **5** (0.40 g, 10%) as a slightly yellow oil: MS (CI, NH_3) *m/e* 482 (M^+ + 1); NMR ($CDCl_3$) δ 8.08 and 7.92 (2 s, 1 H, NCHO, pair of rotamers), 7.56–7.16 (m, 10 H, Ar H), 6.69 (t, 2 H, Ar H, *J* = 8 Hz), 5.00 (s, 2 H, OCH_2), 4.96 (s, 2 H, OCH_2), 4.14 (d, 1 H, C5-β-H, *J* = 13 Hz).

The second compound eluted was the monobenzyl ether **4** (1.56 g, 48%), received as a slightly brown foam: MS (CI, CH_4), *m/e* 392 (M^+ + 1); NMR ($CDCl_3$) δ 8.15 and 7.96 (2 s, 1 H, NCHO, pair of rotamers), 7.36–7.22 (m, 5 H, Ar H), 7.08 (s, 1 H, OH), 6.72 (d, 1 H, Ar H, *J* = 8 Hz), 6.64 (d, 1 H, Ar H, *J* = 8 Hz), 4.88 (s, 2 H, OCH_2), 4.36 (d, 1 H, C5-β-H, *J* = 13 Hz).

(−)-1-(Benzyloxy)-*N*-formyl-4-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]morphinan-6-one (6). A mixture of **4** (1.43 g, 3.65 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (693 mg, 3.84 mmol), and anhydrous K_2CO_3 (3.0 g, 21.71 mmol) was stirred at room temperature in 50 mL of anhydrous DMF under argon atmosphere for 18 h. After filtration and washings with $CHCl_3$, the filtrate was evaporated, the residue dissolved in $CHCl_3$, washed subsequently with 1 N NaOH, H_2O, and brine, dried, and evaporated to give 1.85 g of a brown oil. This product was chromatographed on alumina neutral grade III (CH_2Cl_2) to afford **6** (1.25 g, 64%) as amorphous material: MS (EI), *m/e* 535 (M^+); 8.12–7.92 (m, 3 H, NCHO and Ar H), 7.68–7.30 (m, 8 H, Ar H), 7.07 (d, 1 H, Ar H, *J* = 8 Hz), 6.67 (d, 1 H, Ar H, *J* = 8 Hz), 5.02 (s, 2 H, OCH_2).

(−)-*N*-Formyl-1-hydroxymorphinan-6-one (7). Ten percent Pd/C catalyst (2.2 g) was added to a solution of **6** (700 mg, 1.31 mmol) in 30 mL of glacial AcOH. This mixture was hydrogenated at 50 psi and room temperature for 72 h. The catalyst was filtered off and washed with AcOH, and the filtrate was evaporated. The oily residue was dissolved in $CHCl_3$ and washed with 5% NH_4OH and H_2O and dried, and the solvent was removed in vacuo to yield **7** (295 mg, 79%) as slightly yellow foam: MS (CI, CH_4), *m/e* 286 (M^+ + 1); NMR ($CDCl_3$) δ 8.16 and 7.98 (2 s, 1 H, NCHO, pair of rotamers), 7.04 (dd, 1 H, Ar H, *J* = 8, 8 Hz) 6.84 (d, 1 H, Ar H, *J* = 8 Hz), 6.60 (d, 1 H, Ar H, *J* = 8 Hz), 6.02 (br s, 1 H, OH), 4.90 (m, 1 H, C9-H).

(−)-1-Hydroxymorphinan-6-one (8). A mixture of **7** (170 mg, 0.60 mmol), 13.5 mL of MeOH, and 1.5 mL of 37% HCl was refluxed for 6 h. After evaporation, the residue was dissolved in H_2O, rendered alkaline with 30% NH_4OH, and extracted with a total volume of 20 mL of $CHCl_3$/2-propanol (2:1). The organic layer was washed with brine, dried, and evaporated to give **8** (110 mg, 72%) as colorless oil. A portion of this material was crystallized with MeOH: mp 220–224 °C dec; $[\alpha]^{25}_D$ −139.0° (*c* 0.20, DMF); MS (EI), *m/e* 257 (M^+); IR (KBr) 3420, 3315 and 3300 (OH and NH), 1700 (CO) cm^{-1}; NMR (Me_2SO-d_6) δ 9.17 (s, 1 H, NH or OH), 6.88 (dd, 1 H, Ar H, *J* = 8, 8 Hz), 6.62 (d, 1 H, Ar H, *J* = 8 Hz), 6.54 (d, 1 H, Ar H, *J* = 8 Hz).

Anal. Calcd for $C_{16}H_{19}NO_2$·0.5H_2O: C, 72.15; H, 7.57; N, 5.26. Found: C, 72.04; H, 7.91; N, 5.54.

(−)-1-Hydroxy-*N*-methylmorphinan-6-one (9). A mixture of **8** (100 mg, 0.39 mmol), NaOAc·3H_2O (100 mg, 0.73 mmol), 37% formalin (0.32 mL), 10% Pd/C catalyst (30 mg), and 20 mL of 2 N AcOH was hydrogenated at 45 psi and room temperature for 4 h. The catalyst was filtered off and washed with 2 N AcOH, and the filtrate was evaporated. The residue was dissolved in H_2O, basified with 30% NH_4OH, and extracted with a total volume of 30 mL of $CHCl_3$/2-propanol (2:1). The organic layer was washed with H_2O, dried, and evaporated to give 96 mg of a colorless crystalline residue, which was recrystallized from MeOH to yield pure **9** (68 mg, 64%) (in other experiments it was necessary to pass the pink-colored material through a silica gel column; elution with $CHCl_3$/MeOH/NH_4OH, 90:9:1): mp 272–276 °C dec; $[\alpha]^{25}_D$ −128.9° (*c* 0.46, DMF); MS (CI, CH_4), *m/e* 272 (M^+ + 1); IR (KBr) 3400 (OH), 1700 (CO) cm^{-1}; NMR ($CDCl_3$) δ 6.97 (dd, 1 H, Ar H, *J* = 8, 8 Hz), 6.76 (d, 1 H, Ar H, *J* = 8 Hz), 6.53 (d, 1 H, Ar H, *J* = 8 Hz), 2.44 (s, 3 H, NCH_3).

Anal. Calcd for $C_{17}H_{21}NO_2$·0.5H_2O: C, 72.82; H, 7.91; N, 5.00. Found: C, 72.64; H, 7.52; N, 5.02.

(−)-1-Methoxy-*N*-methylmorphinan-6-one (10). A mixture of **9** (50 mg, 0.18 mmol), anhydrous K_2CO_3 (80 mg, 0.58 mmol), phenyltrimethylammonium chloride (70 mg, 0.41 mmol), and 5 mL anhydrous DMF was stirred at 90 °C (bath temperature)

under argon atmosphere for 4 h. The inorganic solid was filtered off and washed with $CHCl_3$, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2, washed with 1 N NaOH and H_2O, dried, and evaporated to give 50 mg of a semicrystalline residue. This residue was chromatographed on alumina basic grade III (CH_2Cl_2) to yield crystalline **10** (37 mg, 70%). An analytical sample was prepared by recrystallization from MeOH: mp 221–223 °C; $[\alpha]^{25}_D$ −112.8° (*c* 0.40, $CHCl_3$); MS (EI), *m/e* 285 (M^+); IR (KBr) 1705 (CO) cm^{-1}; NMR (Me_2SO-d_6) δ 7.06 (dd, 1 H, Ar H, *J* = 8, 8 Hz), 6.73 (t, 2 H, Ar H, *J* = 8 Hz), 3.72 (s, 3 H, OCH_3), 2.24 (s, 3 H, NCH_3).

Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.75; H, 8.12; N, 4.91. Found: C, 75.45; H, 8.40; N, 4.75.

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Registry No. **1**, 76193-30-1; **2**, 84960-87-2; **3**, 84960-88-3; **4**, 84960-89-4; **5**, 84960-90-7; **6**, 84986-96-9; **7**, 84960-91-8; **8**, 84960-92-9; **9**, 84960-93-0; **10**, 84960-94-1; benzyl bromide, 100-39-0; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4.

Synthesis of the Aryltetralin Lignan Skeleton via the Prins Reaction

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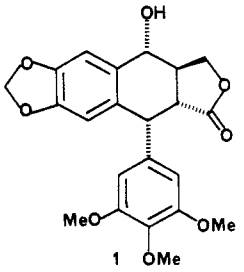
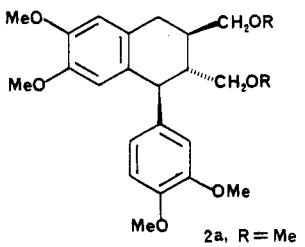
Reaction of a 1,4-diaryl-1-butene (**7**) with paraformaldehyde and the appropriate alkylaluminum halide generates the cation **8**, via addition of formaldehyde to the double bond, which cyclizes to give the aryltetralin **9**. Reaction of 1,4-diphenyl-2-butene (**6a**) with paraformaldehyde and methylaluminum sesquichloride gives the ene adduct **5a**, which reacts further, analogously to **7**, to give **4a** which possesses the aryltetralin lignan skeleton.

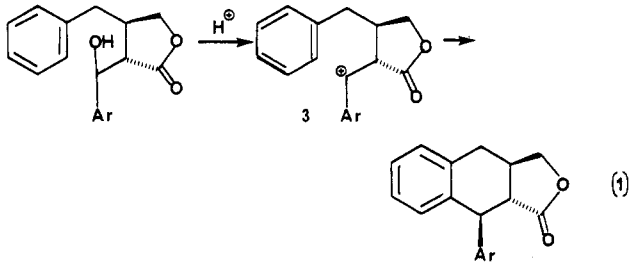
The aryltetralin class of lignans contains a wide variety of compounds including the antitumor agent podophyllotoxin (**1**)[1] and phyltetralin (**2a**).[2] A general route to these





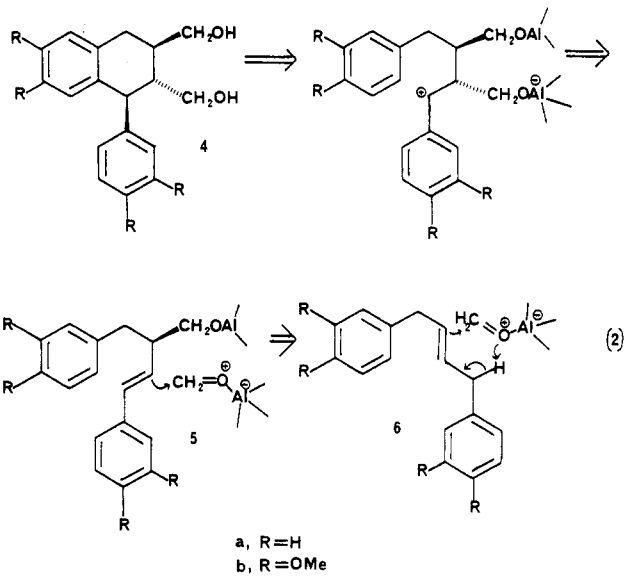
2a, R = Me
2b, R = H

compounds involves the acid-catalyzed cyclization of β-benzyl-α-(hydroxybenzyl)butyrolactones via carbenium ion **3**[2,3] (see eq 1). We were interested in developing alter-



(1)

native routes to these compounds in which carbenium ions analogous to **3** are generated in situ by addition of formaldehyde to the appropriate styrene **5** (see eq 2). This approach is particularly attractive for symmetrical lignans



a, R=H
b, R=OMe

(2)

since the required styrene **5** can itself be constructed in situ from an ene reaction of formaldehyde with 1,4-diaryl-2-butene **6** (see eq 2).

Initial model studies were conducted with 1,4-diaryl-1-butenes (**7**) which are prepared by a Wittig reaction of a dihydrocinnamylphosphonium ylide with a benzaldehyde. Cyclizations to give **9** are carried out in CH_2Cl_2 at 0–20 °C for 30 min with an excess of paraformaldehyde and Lewis acid (see eq 3). The results are summarized in Table I. Good yields of adducts are obtained in all cases except for **7d** and **7f** which contain a methylenedioxy group prone to decomposition during the reaction.[1] The stereochemistry of **9** can be determined by analysis of the NMR spectrum; the doubly benzylic proton of the trans isomer absorbs at δ 3.8–4.0 as a doublet (*J* = 9 Hz) while that of the cis isomer absorbs at δ 4.2–4.4 as a doublet (*J* = 5 Hz).[1]

We have recently shown that alkylaluminum halides are especially effective catalysts for the ene reactions of aldehydes with alkenes since they are proton scavengers as

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