BYPRODUCTS IN THE O-PHENYLTETRAZOLYLATION OF (±)-2,4-DIHYDROXY-N-FORMYLMORPHINAN-6-ONE. ALKYLATION AT C-5.

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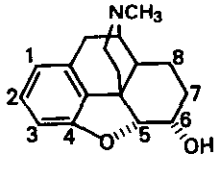
Abstract - O-Alkylation of (±)-2,4-dihydroxy-N-formylmorphinan-6-one (4) with 5-chloro-1-phenyl-1H-tetrazole in DMF in the presence of potassium carbonate afforded substantial amounts of the C-5 alkylated ketones 6 and 7 in addition to the desired ketone 5. The structures of 5, 6 and 7 were supported by chemical correlation and on the basis of spectral data.

2,4-Dihydroxy-N-formylmorphinan-6-one (4) served as a useful intermediate in our total synthesis of 3-deoxy-7,8-dihydromorphine (1)[1,2,3] and in the synthesis of 4-substituted morphinans, 2 and 3.[2,3,4] In these syntheses the 2-OH group was removed after the 4,5-epoxide ring had been closed.



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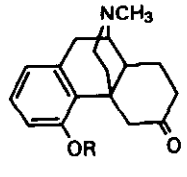

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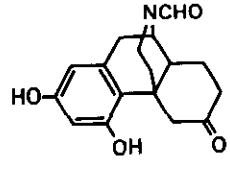
3 R = CH3



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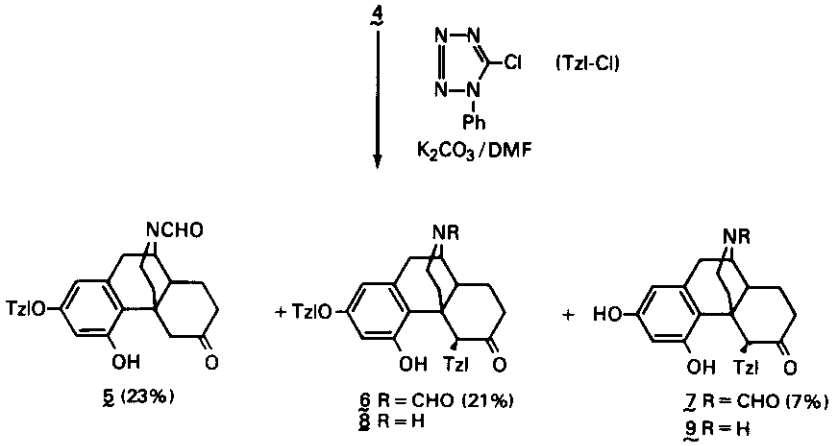
The regioselective deoxygenation of 4 following procedures successfully used by Beyerman's team in the related 2,4-dihydroxy-3-methoxymorphinan series,[5] turned out to be unusually difficult. A tlc analysis of the product mixture obtained after treating 4 with 5-chloro-1-phenyl-1H-tetrazole in DMF in the presence of potassium carbonate showed the presence of 5, 6, and 7 in addition to the starting material. All these compounds were readily obtained in pure form by column chromatographic

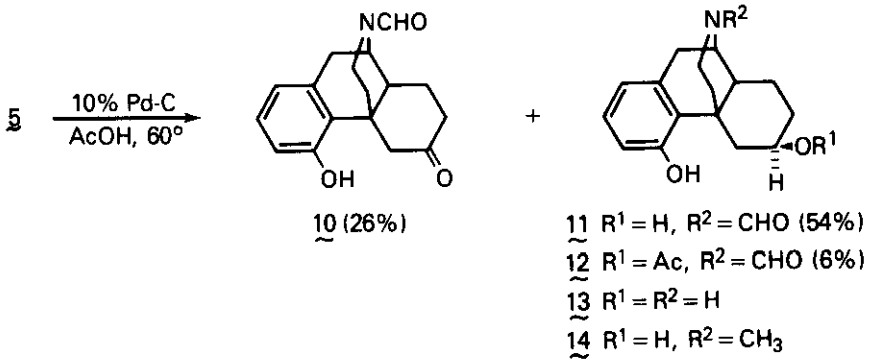
separation. (Scheme 1).

SCHEME 1



The catalytic hydrogenation of 5 over Pd/C catalyst in acetic acid at 60°C, gave the phenol 10, the diol 11, and its acetate 12 (Scheme 2). Phenol 10 was identical by ms, nmr, tlc with the optically active isomer prepared earlier from natural morphine.[6] The diol 11 and the acetate 12 were found to belong to the $C_{6\beta}$-OH series, since acid hydrolysis afforded the same diol 13, which after reductive N-methylation gave diol 14, identical by tlc, nmr spectrum with the β-OH epimer obtained in the optically active series.[7]

SCHEME 2



The monotetrazolylated ketones 5 and 7 were correlated with 6 by further alkylation, and 6 could directly be obtained as the major product from 4 with an excess of the reagent. The nmr spectra of 6 and 7 showed the signal of the proton at C-5 as a sharp singlet at δ 6.35, suggesting that both compounds were C-5 alkylated. The spectral interpretation of N-formylated compound is often complicated by the presence of rotamers[8] and for this reason 6 was hydrolyzed with methanolic HCl to 8, obtained together with 9. Both 8 and 9 showed absorptions for the D_2O exchangeable C-5 proton at δ 6.36 and 6.40, respectively. Model inspections suggest that the N-phenyltetrazolyl substituent has the β-configuration because of the steric situation enforced by the 4-OH group and the relatively rigid nature of the morphinan carbon-nitrogen skeleton. This assignment is in good agreement with the finding of Bös and Fleischhacker, who recently reported similar results for β-substituted 5-methoxymorphinan-6-ones.[9] It is interesting to note that the ketomorphinans of the 2-OH series[10] and their 4-OH isomers[11] afforded under practically identical alkylation conditions the corresponding tetrazolyl ether in good yield, suggesting that the 2,4-dihydroxy-substituted series of ketomorphinans represents a special case.

EXPERIMENTAL PART[3]

General remarks. Physical constants and spectra were determined using the instrumentation indicated. Melting points (m.p.): Thomas-Hoover or Fisher-Johns apparatus (corrected). IR spectra (ν[cm^{-1}]): Beckman IR 4230 Spectrophotometer. NMR spectra ([ppm] relative to internal TMS, Multiplicity: s=singlet, d=doublet, dd=doublet of doublet, q=quartet, m=multiplet, J[Hz]=apparent coupling constant): Varian HR 220 or JOEL LNM-FX 100 spectrometer. Mass spectra (MS) (m/e): Finnigan 1015D spectrometer with a Model 6000 data collection system for chemical ionization (CI) mass spectra or Hitachi Perkin-Elmer RMU-6E spectrometer (70 eV) for electron ionization (EI) mass spectra. Thin layer chromatography (TLC.): silica gel GF, Analtech, Inc. Column chromatography: alumina Woelm N, Act. III, Woelm Pharma. or silica gel 60, 230-400 mesh ASTM, EM Reagent.

N-Formyl-4-hydroxy-2-(1-phenyltetrazol-5-yloxy)morphinan-6-one (5), N-Formyl-4-hydroxy-2-(1-phenyltetrazol-5-yloxy)-5-(1-phenyltetrazol-5-yl)morphinan-6-one (6) and 2,4-Dihydroxy-N-formyl-5-(1-phenyltetrazol-5-yl)morphinan-6-one (7).

A mixture of 4 (3.6 g, 12 mmol), 5-chloro-1-phenyl-1H-tetrazole (2.3 g, 12.7 mmol), anhydrous K_2CO_3 (8.4 g, 60.8 mmol) and DMF (150 ml) was heated at 80 ± 5°C for 16 h under argon. The mixture was filtered and the filtrate was evaporated under high vacuum to give a dark brown residue. This crude material was taken into 200 ml of 2N NaOH and washed with ether. The basic solution was then acidified with concentrated HCl and extracted with $CHCl_3$-:iso-PrOH (3:2). The combined organic solution was washed with brine, dried (Na_2SO_4), and evaporated to give a dark brown gum. This residue

was chromatographed on silica gel ($CHCl_3$:MeOH = 40:1) to afford bistetrazole 6 (1.54 g, 21%): An analytical sample was recrystallized from DMF-MeOH; m.p. 268-270°C; ir(KBr) 3400 (br, OH), 1720 (ketone), 1650 cm^{-1} (amide); nmr (DMSO-d_6, 100 MHz) δ 6.35 (s, 1H, C_5-H, exchangeable with D_2O), 6.70 (d, 1H, ArH, J = 3Hz), 6.72 (d, 1H, ArH, J = 3Hz), 7.84, 8.05 (2s, 1H, HCHO), 10.14 (s, 1H, OH); MS (CI/NH_3) m/e 590 (M^++1). Anal. Calcd for $C_{31}H_{27}N_9O_4 \cdot 0.5$ MeOH: C, 62.47; H, 4.83; N, 20.81. Found: C, 62.56; H, 4.54; N 21.05.

The second product which eluted was collected and recrystallized from DMF-EtOAc to give 5 (1.15 g, 23%): m.p. 254-256°C; ir (KBr) 3400 (br, OH), 1705 (ketone), 1650 cm^{-1} (amide); nmr (DMSO-d_6, 100 MHz) δ 6.65 (d, 1H, ArH, J = 3Hz), 6.75 (d, 1H, ArH, J = 3Hz), 7.53-7.74 (m, 5H, ArH), 7.95, 8.09 (2s, 1H, NCHO), 10.13 (s, 1H, OH); ms (CI/NH_3) m/e 445 (M^+ + 1). Anal. Calc. for $C_{24}H_{23}N_5O_4$: C, 64.71; H, 5.20; N, 15.72. Found: C, 64.67; H, 5.25; N, 15.62.

The third minor product which eluted was collected and recrystallized from 95% EtOH to afford 7 (380 mg, 7%): m.p. > 290°C; ir (KBr) 3400 (br, OH), 1715 (ketone), 1650 cm^{-1} (amide); nmr (DMSO-d_6, 100 MHz) δ 5.97 (d, 1H, ArH, J = 3Hz), 6.05 (d, 1H, ArH, J = 3 Hz), 6.35 (s, 1H, C_5-H, exchangeable with D_2O), 7.55-7.70 (m, 5H, ArH), 7.83, 8.04 (2s, 1H, NCHO), 9.08, 9.22 (2s, 2H, 2OH); ms (CI/NH_3) m/e 446 (M^+ +1). Anal. Calc for $C_{24}H_{23}N_5O_4$: C, 64.71; H, 5.20; N, 15.72. Found: C, 64.58; H, 5.48; N, 15.80.

4-Hydroxy-2-(1-phenyltetrazol-5-yloxy)-5-(1-phenyltetrazol-5-yl)-morphinan-6-one (8).

A mixture of 6 (1.4 g, 2.3 mmol), MeOH (200 ml) and concentrated HCl (20 ml) was refluxed for 6 h. The MeOH was evaporated and the aqueous solution was adjusted to pH 8 and extracted with $CHCl_3$, then $CHCl_3$:iso-PrOH (3:2). The combined organic layer was washed with brine, dried (Na_2SO_4), and evaporated to give an amorphous solid (1.1 g) which contained a mixture of two major products. This crude product was chromatographed on silica gel using ($CHCl_3$-MeOH-concentrated NH_4OH (90:10:1) to give amine 8 (690 mg, 53%). Recrystallization from DMF-MeOH gave an analytical sample: m.p. 244-245°C; ir (KBr) 3420 (br, OH), 3280 (NH), 1720 cm^{-1} (ketone); nmr (DMSO-d_6, 100 MHz) δ 6.36 (s, 1H, C_5-H, exchangeable with D_2O), 6.65 (d, 1H, ArH, J = 3Hz), 6.69 (d, 1H, ArH, J = 3Hz), 7.55-7.75 (m, 10H, ArH); ms (CI/NH_3) m/e 562 (M^+ +1), 418 (base peak, M^+ -144). Anal. Calc for $C_{30}H_{27}N_9O_3 \cdot 0.5$ MeOH: C, 63.42; H, 5.06; N, 21.82 Found: C, 63.42; H, 5.02; N, 21.20.

The other major product was eluted with $CHCl_3$-MeOH-concentrated NH_4OH (50:50:1) to give 9 as a pinkish solid (200 mg, 40%): m.p. > 250°C; ir (KBr) 3400 (OH), 3120 (NH), 1700 cm^{-1} (ketone); nmr (DMSO-d_6, 100 MHz) δ 6.08 (s, 1H, ArH), 6.12 (s, 1H, ArH), 6.40 (s, 1H, C_5-H, exchanged with D_2O), 7.54-7.76 (m, 10H, ArH), ms (CI/NH_3) m/e 418 (M^+ + 1).

N-Formyl-4-hydroxymorphinan-6-one (10), 4,6β-Dihydroxy-N-formylmorphinan-6-one (11), and 6β-Acetoxy-N-formyl-4-hydroxymorphinan-6-one (12).

A mixture of 5 (1.1 g, 2.5 mmol), 10% Pd-C (2 g), and HOAc (80 ml) was hydrogenated at 45 psi at 60-65°C for 2.5 days. The mixture was filtered and washed with HOAc. The filtrate was evaporated and the residue was dissolved in $CHCl_3$. The extract was washed with 10% Na_2CO_3, brine, and dried (Na_2SO_4).

Evaporation of solvent gave a foam (1.2 g) which was chromatographed on silica gel ($CHCl_3$:MeOH = 40:1, 600 ml, then 20:1, 500 ml) to afford three products. The first fraction gave 12 (48 mg, 6%) which was recrystallized from MeOH: mp 267-269°C; ir (KBr) 3150 (br , OH), 1730 (ester), 1650 cm^{-1} (amide); nmr (DMSO-d_6, 100 MHz) δ 1.91 (s, 3H, $OCOCH_3$), 6.48-6.62 (m, 2H, ArH), 6.92 (dd, 1H, ArH, J = 7, 7Hz), 7.87, 8.00 (2s, 1H, NCHO); ms (CI/NH_3) m/e 330 (M^+ +1). Anal. Calc for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 68.97; H, 7.27; N, 3.94.

The second fraction gave 10 (182 mg, 26%) which was recrystallized from MeOH: mp 260-262°C; ir (KBr) 3250, 3400 (OH), 1705 (ketone), 1650 cm^{-1} (amide); nmr (DMSO-d_6, 100 MHz) δ 6.48-6.58 (m, 2H, ArH), 6.88 (dd, 1H, ArH, J = 8, 8 Hz), 7.92, 8.07 (2s, 1H, NCHO), 9.43 (s, 1H, OH); MS (CI/NH_3) m/e 286 (M^+ + 1). Anal. Calc for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.33; H, 6.50; N, 4.74.

The third fraction gave the alcohol 11 (380 mg, 54%) which was recrystallized from $CHCl_3$: mp 253-255°C; ir (KBr) 3400 (br, OH), 1640 cm^{-1} (amide); nmr (DMSO-d_6, 100 MHz) δ 3.58 (d, 1H), C_5-H, J = 13 Hz), 4.30 (d, 1H, alcoholic OH, J = 4 Hz, exchange with D_2O), 6.49 (d, 1H, ArH, J = 7 Hz), 6.88 (dd, 1H, ArH, J = 7, 7 Hz), 7.88, 8.02 (2s, 1H, NCHO), 9.24 (s, 1H, phenolic OH); ms (CI/NH_3) m/e 288 (M^+ +1). Anal. Calc for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.26; H, 7.35; N, 4.78.

4,6β-Dihydroxy-N-methylmorphinan (14)

A mixture of 13·HCl (151 mg, 0.51 mmol), 37% HCHO (0.17 ml, 2.2 mmol), NaOAc (210 mg, 2.56 mmol), 10% Pd-C (32 mg), and 2N HOAc (21 ml) was hydrogenated at 45 psi at room temperature for 6 h. The mixture was filtrated and the filtrate was adjusted to pH 8 with concentrated NH_4OH and extracted with $CHCl_3$. The combined $CHCl_3$ solution was washed with brine, dried (Na_2SO_4), and evaporated to give 117 mg of foam. This crude product was passed through short alumina column ($CHCl_3$:MeOH = 20:1) to afford 14 (85 mg, 61%) which was recrystallized from $CHCl_3$: mp 249-251°C; ir (KBr) 330 cm^{-1} (br, OH); nmr (DMSO-d_6, 100 MHz) δ 2.19 (s, 3H, NCH_3), 4.20 (d, 1H, J = 5 Hz), 6.43-6.52 (m, 2H, ArH), 6.80 (dd, 1H, ArH, J = 7, 7 Hz), 9.00 (s, 1H, phenolic OH); ms (EI) m/e 273 (M^+). Anal. Calc for $C_{17}H_{23}NO_2.1/4\ H_2O$: C, 73.47; H, 8.52; N, 5.04. Found C, 73.52; H, 8.38; N, 4.84.

4,6β-Dihydroxymorphinan Hydrochloride (13·HCl).

Compound 11 (215 mg, 0.75 mmol) was refluxed in a mixture of 20% HCl (2 ml) and MeOH (10 ml) to give a white solid. The crude salt was recrystallized from MeOH to yield 13·HCl·1/2CH_3OH (192 mg, 87%): mp > 300°C; ir (KBr) 3300 cm^{-1} (br, OH); nmr (DMSO-d_6, 100 MHz) δ 4.39 (d, 1H, J = 5 Hz) 6.54 (d, 1H, ArH, J = 7.5 Hz), 6.62 (d, 1H, ArH, J = 7.5 Hz) 6.92 (dd, 1H, ArH, J = 7.5 Hz), 8.92 (br s, 2H, NH_2^+), 9.41 (s, 1H, phenolic OH); ms (EI) m/e 259 (M^+). Anal. Calc for $C_{16}H_{21}NO_2$·HCl·1/2 CH_3OH: C, 63.55; H, 7.76; N, 4.49; Cl, 11.36. Found: C, 63.80; H, 7.45; N, 4.45; Cl, 11.59.

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