Synthesis of Metabolites of 3-*O*-*t*-Butylmorphine

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The synthesis of 2-hydroxymethyl-2-propylmorphine (**5**) and 2-hydroxymethyl-2-propylnormorphine (**7**), the major rat urinary metabolites of 3-*O*-*t*-butylmorphine (**3**) are described.

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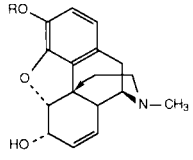
We have previously reported [1] on the synthesis and pharmacology of the *t*-butyl ether of morphine **3**. Metabolic studies in rats have shown [2] that this compound, in contrast to codeine (**2**), failed to undergo *in vivo* *O*-dealkylation to morphine (**1**). The *t*-butyl group in **3** effectively eliminated the *O*-dealkylation of this compound as a major metabolic pathway.

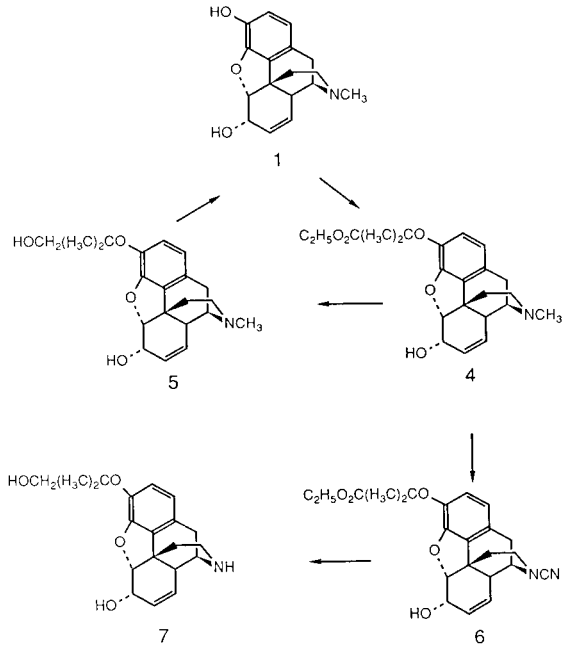


1, R = -H
2, R = -CH$_3$
3, R = -C(CH$_3$)$_3$

The initial step in the biotransformation of **3** is *N*-demethylation. Besides the nor-compound, two additional metabolites of 3-*O*-*t*-butylmorphine (**3**) have been isolated from rat urine, purified by gas chromatography and tentatively identified by mass spectroscopy as 2-hydroxymethyl-2-propylmorphine **5** and 2-hydroxymethyl-2-propylnormorphine (**7**) [2]. Since formation of **5** and **7** represent an unusual hydroxylation at an unactivated methyl group, it seemed desirable to confirm the structure assignment by synthesis. In addition, the present work was undertaken to provide reference samples.

Compounds **4-7** were prepared in accordance with Scheme 1. Thus, 2-ethoxycarbonyl-2-propylmorphine (**4**) was prepared from morphine (**1**) with 2-bromoisobutyrate in ethanol in the presence of sodium ethoxide. Reduction of the ester **4** with lithium aluminum hydride in refluxing tetrahydrofuran afforded the desired crystalline alcohol **5**. The spectral properties of this compound were in full agreement with the assigned structure. Further corroboration of this structure assignment was achieved by dealkylation with pyridine hydrochloride [3] to give morphine (**1**), identical in all respects (mp, mmp, uv and ms) with an authentic sample [4]. When the ester **4** was treated with cyanogen bromide in chloroform [5], the *N*-cyano derivative **6** was formed in good yield. Finally, treatment of **6** with lithium aluminum hydride in refluxing tetrahydrofuran gave the nor-compound **7** [6].

Scheme 1



The synthetic compounds **5** and **7** prepared by the above Scheme were compared by mass spectroscopy with samples obtained from metabolism studies and were found to be identical [2]. These findings confirm the aforementioned metabolic results.

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 Cary Model 14 spectrophotometer. Infrared spectra were determined with a Beckman Model IR 9 spectrophotometer. Nuclear magnetic resonance spectra were measured with a Varian A-60 or HA-100 spectrometer and recorded in δ values with deuteriochloroform as the solvent 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.

7,8-Didehydro-4,5α-epoxy-3-(2-ethoxycarbonyl-2-propyloxy)-17-methylmorphinan-6α-ol (**4**).

Sodium (0.245 g-atom) was dissolved in 25 ml of ethanol (absolute) and to the solution 3.1 g (0.011 mole) of morphine (**1**) and 2.1 g (0.011 mole) of ethyl 2-bromoisobutyrate were added. After heating at reflux for 16 hours the solvent was removed under reduced pressure and the residue

was dissolved in ethyl acetate (200 ml). The ethyl acetate solution was washed with 2*N* sodium hydroxide (2 x 10 ml), then with water (3 x 10 ml) and dried (magnesium sulfate). Removal of the solvent and distillation of the residue gave 2.93 g (68%) of **4**, bp 220-227° (0.05 mm), $[\alpha]_D^{25}$ -107.0° (c = 0.94 methanol); ir (chloroform): 3500, 3000, 1730 and 1600 cm^{-1}; uv (95% ethanol): max 209 mμ (ε 52958), infl 240 (11348), infl 275 (4539) and max 283 (4880); nmr (deuteriochloroform): δ 6.66, 6.46 (AB, 2, J = 8.5 Hz, ArH), 5.66 and 5.24 (m, m, 2, J_{cis} = 10 Hz, -CH = CH-), 4.25 (q, 2, J = 7.5 Hz, $-CH_2-$), 2.40 (s, 3, $-NCH_3$), 1.55 (s, 3, $-CH_3$), 1.42 (s, 3, $-CH_3$) and 1.29 (tr, 3, J = 7.5 Hz, $-CH_3$); ms: m/e 399 [M⁺].

Anal. Calcd. for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.38; N, 3.51. Found: C, 68.96; H, 7.21; N, 3.22.

7,8-Didehydro-4,5α-epoxy-3-(2-hydroxymethyl-2-propyloxy)-17-methylmorphinan-6α-ol (**5**).

To a suspension of 2.0 g of lithium aluminum hydride in 50 ml of anhydrous tetrahydrofuran was added dropwise a solution of 4.0 g (0.011 mole) of 7,8-didehydro-4,5α-epoxy-3-(2-ethoxycarbonyl-2-propyloxy)-17-methylmorphinan-6α-ol (**4**) in 50 ml of anhydrous tetrahydrofuran. After the mixture had been refluxed for 16 hours, it was cooled to room temperature and ethyl acetate followed by water were cautiously added dropwise. The resulting suspension was filtered and the filtrate was dried (magnesium sulfate). Removal of the solvent under reduced pressure gave the crude **5**, which after recrystallization from acetone--ether afforded 0.894 g (25%) of **5**, mp 125-126°, $[\alpha]_D^{25}$ -101.0° (c = 1.05, methanol); ir (chloroform): 3525, 3020, 2950 and 1600 cm^{-1}; uv (95% ethanol): max 210 mμ (ε 29460), infl 238 (5230), infl 278 (1695) and max 285 (1910); nmr (deuteriochloroform): δ 6.70, 6.60 (AB, 2, J = 8.0 Hz, ArH), 5.65 and 5.40 (m, m, 2, J_{cis} = 10 Hz, -CH=CH), 4.88 (m, 1, =C*H*OH), 3.40 (s, 2, $-CH_2OH$), 2.45 (s, 3, $-NCH_3$), 1.35 (s, 3, $-CH_3$) and 1.25 (s, 3, $-CH_3$); ms: m/e 357 [M⁺], 326, 308, 285, 215, 162, 124, 115 and 44.

Anal. Calcd. for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.21; H, 7.64; N, 3.83.

7,8-Didehydro-17-cyano-4,5α-epoxy-3-(2-ethoxycarbonyl-2-propyloxy)-morphinan-6α-ol (**6**).

To a solution of 1.75 g of cyanogen bromide in 35 ml of chloroform [5] was added a solution of 6.65 g (0.016 mole) of 7,8-didehydro-4,5α-epoxy-3-(2-ethoxycarbonyl-2-propyloxy)-17-methylmorphinan-6α-ol (**4**) in 10 ml of chloroform. After the mixture had been refluxed for 3 hours, it was cooled to room temperature, diluted with 100 ml chloroform and washed successively with 1*N* hydrochloric acid (2 x 50 ml), 2*N* sodium hydroxide (100 ml) and water (100 ml). After drying (magnesium sulfate) the solvent was removed under reduced pressure to give the crude **6**, mp 137-138°, $[\alpha]_D^{25}$ -143.2° (c = 1.03, methanol); ir (chloroform): 3500, 3020, 1733 and 1600 cm^{-1}; uv (95% ethanol): max 214 mμ (ε 26600), infl 245 (3600), infl 280 (1775) and max 286 (1980).

Anal. Calcd. for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82. Found: C, 66.92; H, 6.30; N, 6.72.

7,8-Didehydro-4,5α-epoxy-3-(2-hydroxymethyl-2-propyloxy)morphinan-6α-ol (**7**).

To a suspension of 3.0 g of lithium aluminum hydride in 50 ml of anhydrous tetrahydrofuran was added dropwise a solution of 2.06 g (0.005 mole) of 7,8-didehydro-17-cyano-4,5α-epoxy-3-(2-ethoxycarbonyl-2-propyloxy)morphinan-6α-ol (**6**) in 50 ml of anhydrous tetrahydrofuran. After the mixture had been heated at reflux for 16 hours, it was cooled to room temperature and 20 ml of saturated sodium chloride solution was added dropwise cautiously. The mixture was heated on a water bath for 1 hour then filtered with the aid of Celite and the filtrate was concentrated to give 1.39 g (81%) of **7** as an amorphous substance, homogeneous on tlc but resistant to crystallization, $[\alpha]_D^{25}$ -77.4° (c = 1.23 methanol); ir (chloroform): 3520, 3000, 2700 and 1600 cm^{-1}; uv (95% ethanol): max 212 mμ (ε 26100), infl 235 (5400), infl 2.78 (1600) and max 285 (1800); nmr (deuteriochloroform): δ 6.68, 660 (AB, 2, J = 8 Hz, ArH), 5.70 and 5.27 (m, m, 2, J_{cis} = 10 Hz, -CH=CH), 4.90 (d, 1, J = 6.0 Hz, -OCH=), 4.22 (m, 1, =C*H*OH), 3.42 (s, 2, $-CH_2OH$), 1.32 (s, 3, $-CH_3$) and 1.28 (s, 3, $-CH_3$); ms: m/e 343 [M⁺], 312, 294, 285, 271, 201, 150, 148, 115, 110, 81, 71, 57, 42 and 31.

Anal. Calcd. for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34; N, 4.08. Found: C, 70.03; H, 7.57; N, 4.00.

Conversion of 7,8-Didehydro-4,5α-epoxy-(2-hydroxymethyl-2-propyloxy)-17-methylmorphinan-6α-ol (**5**) to Morphine (**1**).

A mixture of 0.2 g (0.0006 mole) of 7,8-didehydro-4,5α-epoxy-3-(2-hydroxymethyl-2-propyloxy)-17-methylmorphinan-6α-ol (**5**) and 0.5 g of pyridine hydrochloride [3] was heated at 220° (oil bath temperature) with stirring under nitrogen for 15 minutes. After cooling in an ice-bath it was treated with dilute ammonium hydroxide and was taken to dryness *in vacuo*. The residue was dissolved in ethyl acetate, washed with water and dried (magnesium sulfate). The solvent was removed under reduced pressure and the crude product after separation by preparative tlc [on silica gel plates using chloroform: methanol (4:1) for development] gave 0.071 g (44%) of morphine (**1**), which upon recrystallization from ethanol melted at 251-252° (lit [4] mp 251-256°). Its mmp with an authentic sample was undepressed and its spectroscopic properties (uv and ms) were identical with those of an authentic sample of morphine (**1**).

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