

## 215. Total Synthesis of ( $\pm$ )-3-Deoxy-7,8-dihydromorphine

Preliminary Communication

by Fu-Lian Hsu, Kenner C. Rice and Arnold Brossi<sup>1)</sup>

Medicinal Chemistry Section, Laboratory of Chemistry, National Institute of Arthritis, Metabolism and Digestive Diseases, National Institutes of Health, Bethesda, Maryland 20205, USA

(18.VIII.80)

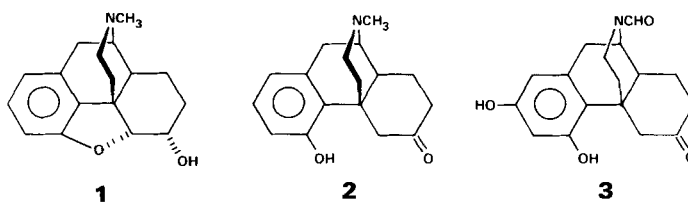
### Totalsynthese des ( $\pm$ )-3-Desoxy-7,8-dihydromorphins

#### Zusammenfassung

( $\pm$ )-3-Desoxy-7,8-dihydromorphin (( $\pm$ )-**1**) wurde aus 3,5-Dihydroxyphenylessigsäure und 3-Methoxyphenäthylamin über elf isolierte Zwischenstufen totalsynthetisiert. Als Schlüsselverbindung diente dabei ( $\pm$ )-*N*-Formyl-2,4-dihydroxymorphinan-6-on (**3**). Das daraus über mehrere Zwischenstufen erhaltene ( $\pm$ )-3-Desoxy-6, *O*-didehydro-7,8-dihydromorphin (= *N*-Methyl-4,5a-epoxymorphinan-6-on, **12**), ergab bei der Reduktion mit *Lithiumselectrid* stereospezifisch das gewünschte ( $\pm$ )-**1**, während bei der katalytischen Reduktion und unter energischeren Bedingungen ( $\pm$ )-4-Hydroxy-*N*-methilmorphinan-6-on (( $\pm$ )-**2**) anfiel. Damit ist die Totalsynthese von **2** realisiert worden.

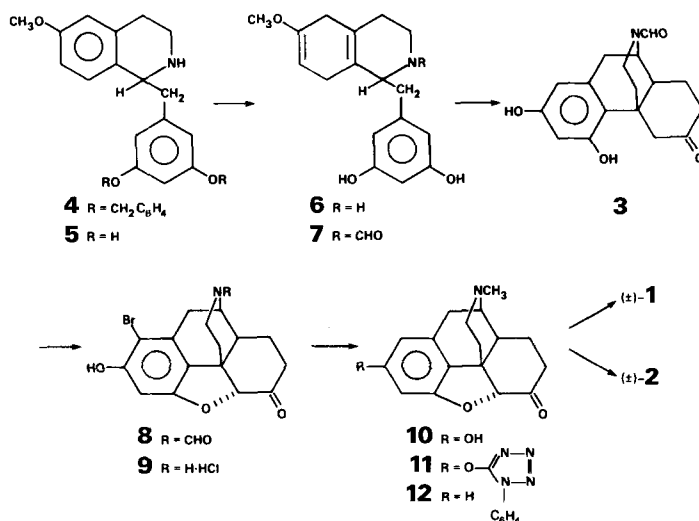
3-Deoxy-7,8-dihydromorphine (**1**), easily prepared from 7,8-dihydromorphine or morphine by catalytic hydrogenation of its *N*-phenyltetrazolyl ether derivative [1], represents an important intermediate for preparing other 3-deoxy opioids [1]. It is also a convenient source for preparing 4-hydroxymorphinan-6-ones [2] [3], needed to further explore the structure-activity relationship of differently oxygenated morphinan derivatives. We now would like to report the first total synthesis of ( $\pm$ )-3-deoxy-7,8-dihydromorphine (( $\pm$ )-**1**).

Scheme 1



<sup>1)</sup> To whom correspondence should be addressed.

Scheme 2



The synthetic plan chosen was much influenced by the chemistry reported by *Beyerman et al.* in their syntheses of dihydrothebainone and related congeners [4] [5] and our own findings, made particularly in connection with the conversion of **1** into **2** and its reconversion into **1** [2] (s. *Scheme 1*). An analysis of these investigations suggested synthesis of the dihydroxy ketone **3**, an intermediate which would allow manipulation of the aromatic moiety in several ways to achieve our objective.

A total synthesis of racemic ketone **3** and its successful conversion into 3-deoxy-7,8-dihydromorphine ((±)-**1**), was achieved as described in the *Scheme 2*. Direct condensation of 3,5-dihydroxyphenylacetic acid obtained from dimethyl 3-oxo-1,5-pentanedioate (= dimethyl 1,3-acetonedicarboxylate) [6] with 3-methoxyphenethylamine gave the corresponding amide in very low yield and suggested protection of phenolic groups prior to reaction. 3,5-Dibenzyloxyphenylacetic acid, m.p. 120–121° (benzene/petroleum ether)<sup>2)</sup>, obtained in the usual fashion afforded the amide, m.p. 101–102° (CHCl<sub>3</sub>/ether) in 89% yield, after heating with 3-methoxyphenethylamine. Cyclization of this amide to the corresponding 3,4-dihydroisoquinoline by the conventional *Bischler-Napieralski* procedure, followed by a sodium borohydride reduction and treatment with methanolic hydrogen chloride afforded the tetrahydroisoquinoline **4** as its hydrochloride in 89% yield, m.p. 195–196.5° (CHCl<sub>3</sub>/ether). Catalytic debenzoylation of **4**·HCl over 10% Pd/C in 95% ethanol gave the crystalline diphenol **5**·HCl in 90% yield, m.p. 253–255° (dec., H<sub>2</sub>O). Both the free base **4** and the hydrochloride salt of **5** underwent facile *Birch* reduction with a large excess of Li in liquid NH<sub>3</sub> at –60° in the presence of *t*-butyl alcohol and tetrahydrofuran to afford the microcrystalline dihydro base **6**

<sup>2)</sup> All new compounds were characterized by elemental analysis and show the expected spectroscopic features.

(90–95%), m.p. 199–200° (dec., ethanol/ethyl acetate [IR.<sup>3</sup>] (KBr): 1670, 1700 (dihydroanisole) [7], 3200 (NH). – <sup>1</sup>H-NMR.<sup>3</sup>) (DMSO-*d*<sub>6</sub>): 3.44 (*s*, 3 H, CH<sub>3</sub>O); 4.64 (*m*, 1 H, 1 vinylic H); 6.04 (*m*, 3 H, 3 arom. H); 9.00 (br. *s*, 2 H, 2 HO). – MS.: 287 (*M*<sup>+</sup>). Treatment of the base **6** with refluxing ethyl formate in *N,N*-dimethylformamide gave the formamide **7**<sup>4</sup>) (82%), m.p. 213–215° (*N,N*-dimethylformamide/CHCl<sub>3</sub>) [IR. (KBr): 1650 (NHCO), 1670, 1700 (dihydroanisole) [7]. – <sup>1</sup>H-NMR. (DMSO-*d*<sub>6</sub>): 3.48 (*s*, 3 H, CH<sub>3</sub>O); 4.70 (*m*, 1 H, 1 vinylic H); 6.00 (*m*, 3 H, 3 arom. H); 7.43 and 7.90 (2 *s*, 1 H, NCHO); 8.97 and 9.05 (2 *s*, 2 H, 2 HO). – MS.: 315 (*M*<sup>+</sup>). Compound **7** could be cyclized with conc. HCl-solution in refluxing diethyl ether to afford 2,4-dihydroxy ketone **3** in 91% yield, m.p. 316–319° (dec., *N,N*-dimethylformamide/H<sub>2</sub>O) [IR. (KBr): 1660 (NCHO), 1705 (CO), 3300 (OH). – <sup>1</sup>H-NMR. (DMSO-*d*<sub>6</sub>): 3.97 (*d*, *J* = 13 Hz, 1 H, H–C(5)); 5.97 (*d*, *J* = 2 Hz, 1 H, 1 arom. H); 6.07 (*d*, *J* = 2 Hz, 1 H, 1 arom. H); 7.98 and 8.11 (2 *s*, 1 H, NCHO); 9.05 and 9.33 (2 *s*, 2 H, 2 HO). – MS.: 301 (*M*<sup>+</sup>). Closure of the oxide bridge of the difficultly soluble ketone **3** was achieved by bromination of **3** in acetic acid at room temperature (1 g of **3** in 200 ml of acetic acid) with 2.5 mol of bromine, followed by evaporation of the solvent and treatment with 10% NaOH-solution, to afford a mixture of brominated materials from which the bromo ketone **8** could be isolated as methanol insoluble material (39%), m.p. >240° (dec.) [IR. (KBr): 1640 (NCHO), 1725 (CO), 3420 (OH). – <sup>1</sup>H-NMR. (DMSO-*d*<sub>6</sub>): 4.92 (*s*, 1 H, H–C(5)); 6.42 (*s*, 1 H, 1 arom. H); 7.98 and 8.05 (2 *s*, 1 H, NCHO); 10.2 (*s*, 1 H, HO). – MS.: 377 (*M*<sup>+</sup>), 379 (*M*<sup>+</sup> + 2)]. Hydrolysis of **8** with 10% conc. HCl-solution in CH<sub>3</sub>OH afforded **9** (86%), m.p. >270° (dec., CH<sub>3</sub>OH) [IR. (KBr): 1715 (CO), 3440 (OH). – <sup>1</sup>H-NMR. (D<sub>2</sub>O): 5.14 (*s*, 1 H, H–C(5)); 6.62 (*s*, 1 H, 1 arom. H). – MS.: 349 (*M*<sup>+</sup>), 351 (*M*<sup>+</sup> + 2)]. Concomitant [8] debromination and *N*-methylation of **9** were carried out by hydrogenating 1 mmol of **9**, in the presence of 0.3 ml of 37% formaldehyde, 30 ml of 2*N* acetic acid, 5 mmol of sodium acetate, and 50 mg of 10% Pd/C to afford **10** in 67% yield, m.p. 265–268° (dec., CH<sub>3</sub>OH) [IR. (KBr): 1720 (CO), 3420 (OH). – <sup>1</sup>H-NMR. (DMSO-*d*<sub>6</sub>): 2.28 (*s*, 3 H, CH<sub>3</sub>N); 4.76 (*s*, 1 H, H–C(5)); 6.07 (*m*, 2 H, 2 arom. H); 9.16 (br. *s*, 1 H, HO). – MS.: 285 (*M*<sup>+</sup>). – **10** · HCl: m.p. >250° (dec., ethanol)]. Dehydroxylation of **10** could be accomplished *via* the *N*-phenyltetrazolyl ether derivative **11** (88%), m.p. 207–208° (ethanol) by catalytic reduction over 10% Pd/C in acetic acid. (±)-3-Deoxy-6, *O*-didehydro-7,8-dihydromorphine (= *N*-methyl-4,5-*α*-epoxymorphinan-6-one; **12**), m.p. 213–215° (benzene/petroleum ether), obtained in 69% yield after recrystallization was identical by TLC., IR., NMR., and MS. with material prepared from natural morphine [1]. (±)-4-Hydroxy-*N*-methylmorphinan-6-one ((±)-**2**), m.p. 243–245° (benzene) was obtained from **11** when the reduction was carried out at 50° for three days. Reduction of **12** with lithium tri(*s*-butyl)borohydride in tetrahydrofuran gave a quantitative yield of (±)-3-deoxy-7,8-dihydromorphine ((±)-**1**), m.p. 57–59° ((±)-**1** · HCl: m.p. 266–268°, CH<sub>3</sub>OH). None of the epimeric C(6) hydroxyl compound (HO-*C*(6)) was found by HPLC. [*μ*Bondapak (Water Associates), CH<sub>3</sub>OH/1% acetic acid in H<sub>2</sub>O 1:9, with UV. detection at 250 nm].

<sup>3</sup>) IR. spectra:  $\bar{\nu}_{\max}$  in cm<sup>-1</sup>. <sup>1</sup>H-NMR. spectra: at 100 MHz or 220 MHz; internal standard tetramethylsilane ( $\delta$  = 0 ppm); *s* = singlet, *d* = doublet, *J* = spin-spin coupling constant.

<sup>4</sup>) Compound **7** existed as a pair of rotamers according to TLC. and <sup>1</sup>H-NMR.

We would like to thank Mr. *J. P. Choe* for technical assistance; Dr. *J. W. Scott* from *Hoffmann-La Roche, Inc.*, New Jersey, for preparation of large amounts of 3-methoxyphenethylamine used in this work; and to Dr. *A. E. Jacobson* from our laboratory, for helpful advice.

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