215. Total Synthesis of (±)-3-Deoxy-7,8-dihydromorphine

Preliminary Communication

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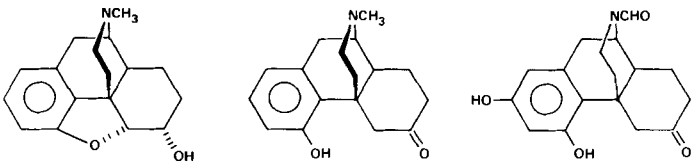
Totalsynthese des (±)-3-Desoxy-7,8-dihydromorphins

Zusammenfassung

(±)-3-Desoxy-7,8-dihydromorphin ((±)-**1**) wurde aus 3,5-Dihydroxyphenylessigsäure und 3-Methoxyphenäthylamin über elf isolierte Zwischenstufen totalsynthetisiert. Als Schlüsselverbindung diente dabei (±)-*N*-Formyl-2,4-dihydroxymorphinan-6-on (**3**). Das daraus über mehrere Zwischenstufen erhaltene (±)-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 (±)-**1**, während bei der katalytischen Reduktion und unter energischeren Bedingungen (±)-4-Hydroxy-*N*-methylmorphinan-6-on ((±)-**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 (±)-3-deoxy-7,8-dihydromorphine ((±)-**1**).

Scheme 1



1 **2** **3**

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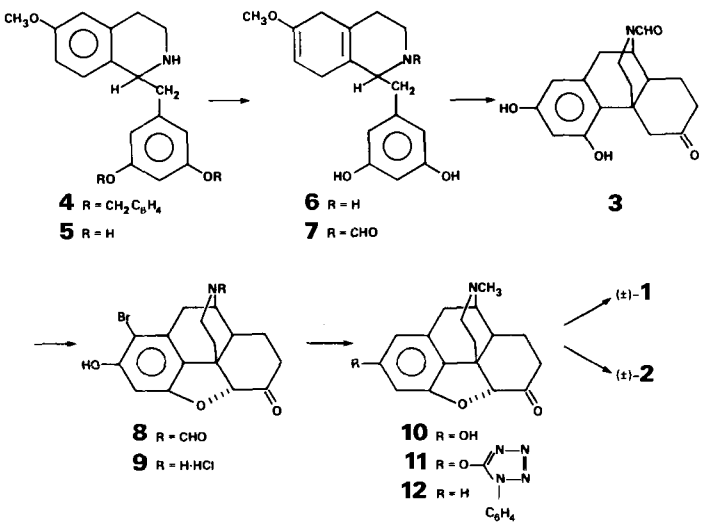
Scheme 2



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)[2]), obtained in the usual fashion afforded the amide, m.p. 101–102° ($CHCl_3$/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° ($CHCl_3$/ether). Catalytic debenzylation 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_2O). Both the free base **4** and the hydrochloride salt of **5** underwent facile *Birch* reduction with a large excess of Li in liquid NH_3 at −60° in the presence of *t*-butyl alcohol and tetrahydrofuran to afford the microcrystalline dihydro base **6**

[2]) 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.[3]) (KBr): 1670, 1700 (dihydroanisole) [7], 3200 (NH). – ^{1}H-NMR.[3]) (DMSO-d_6): 3.44 (*s*, 3 H, CH_3O); 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^+)]. Treatment of the base **6** with refluxing ethyl formate in *N*,*N*-dimethylformamide gave the formamide **7**[4]) (82%), m.p. 213–215° (*N*,*N*-dimethylformamide/$CHCl_3$) [IR. (KBr): 1650 (NHCO), 1670, 1700 (dihydroanisole) [7]. – ^{1}H-NMR. (DMSO-d_6): 3.48 (*s*, 3 H, CH_3O); 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^+)]. 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_2O) [IR. (KBr): 1660 (NCHO), 1705 (CO), 3300 (OH). – ^{1}H-NMR. (DMSO-d_6): 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^+)]. 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). – ^{1}H-NMR. (DMSO-d_6): 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^+), 379 ($M^+ + 2$)]. Hydrolysis of **8** with 10% conc. HCl-solution in CH_3OH afforded **9** (86%), m.p. >270° (dec., CH_3OH) [IR. (KBr): 1715 (CO), 3440 (OH). – ^{1}H-NMR. (D_2O): 5.14 (*s*, 1 H, H–C(5)); 6.62 (*s*, 1 H, 1 arom. H). – MS.: 349 (M^+), 351 ($M^+ + 2$)]. 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_3OH) [IR. (KBr): 1720 (CO), 3420 (OH). – ^{1}H-NMR. (DMSO-d_6): 2.28 (*s*, 3 H, CH_3N); 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^+). – **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-4,5α-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_3OH). None of the epimeric C(6) hydroxyl compound (HO_β–C(6)) was found by HPLC. [*µBondapak (Water Associates)*, CH_3OH/1% acetic acid in H_2O 1:9, with UV. detection at 250 nm].

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

[4]) Compound **7** existed as a pair of rotamers according to TLC. and ^{1}H-NMR.

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