# Synthesis of 5a,11b-Propanonaphtho[1,2-*e*][1,2]oxazepines as Potential Opioid Analgesics

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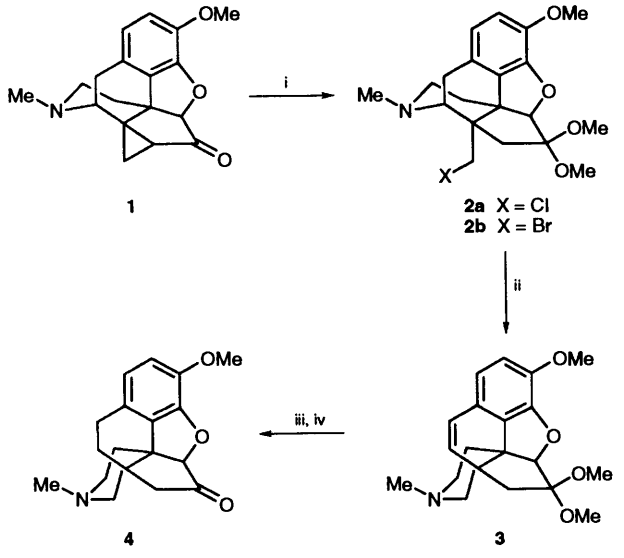
5a,11b-Propanonaphtho[1,2-*e*][1,2]oxazepines have been prepared from dihydro-7,14-cyclocodeinone by the following reaction path: nucleophilic cyclopropane-ring opening, *N*-oxide formation, Cope reaction and intramolecular *O*-alkylation. The skeleton of the resulting compounds which have potential as analgesics, is closely similar to that of the parent morphinan, although there is a novel annulation of the nitrogen-containing ring which is further expanded to an oxazepine.

In previous papers, we have reported on the synthesis of novel opioid analgesics which are structurally related to the morphine series but are characterized by a divergent annulation of the piperidine ring.[1,2] The target compound **4** is available in a four-step synthesis starting from dihydro-7,14-cyclocodeinone **1** (see Scheme 1).[2] The key step of this sequence is a nucleophilic

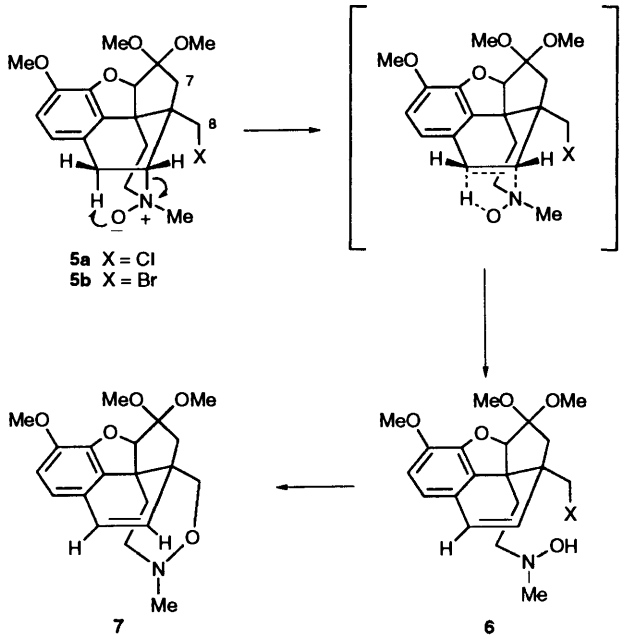



**Scheme 1** *Reagents and conditions:* i, $SOCl_2$, MeOH, $CH_2Cl_2$ ($PBr_3$, MeOH, $CH_2Cl_2$); ii, KOH, MeOH, heat; iii, $H_2$, Pd–C, AcOH, 80 °C; iv, HCl (2 mol $dm^{-3}$)

opening of the cyclopropane ring by thionyl chloride in methanol–dichloromethane to **2a** (or by phosphorus tribromide in methanol–dichloromethane to **2b**) followed by an intramolecular Hofmann degradation to **3**.

In preliminary pharmacological studies of **3** and **4** (including derivatives) using μ-opioid receptors of the rat cerebral cortex, we have found that our compounds are active whereby the dislocation of the nitrogen,* being essential for receptor binding, is well tolerated.[3]

Stimulated by these results, we decided to synthesize *O*-homologues, using a comparable pathway: Cope reaction, performed on the corresponding *N*-oxide **5**, should result in the formation of the hydroxylamine **6** which can further be *O*-alkylated yielding the oxazepine **7** (see Scheme 2). This *O*-homologue would furnish a modified representation of the




**Scheme 2**

nitrogen binding site. Considering the fact that the Cope reaction represents a stereoselective *syn* process,[4] this strategy was created under the presumption of a successful approach to the required *N*-oxide stereoisomer **5**.

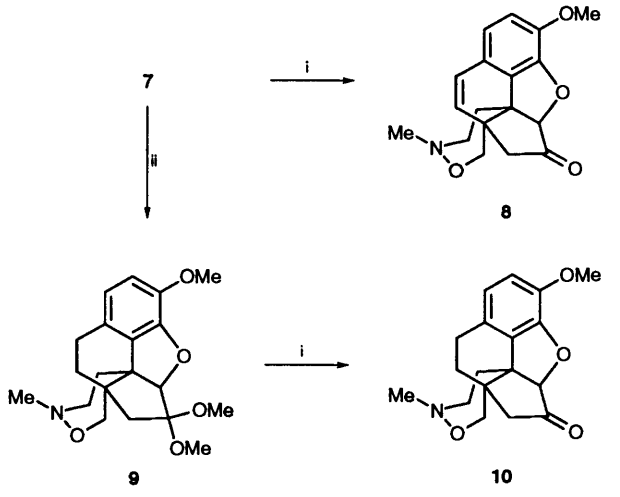
Previously, we have prepared *N*-oxides in the C-nor-morphinan series, a practicable method to mask the amine function during critical synthetic steps. In this connection, we observed that only one *N*-oxide stereoisomer was formed, indicated by a single *N*-methyl group signal in the $^1H$ NMR spectrum, although the configuration of the *N*-oxide was not clear at this stage.[5] Applied to **2a** (or **2b**, respectively) the *N*-oxides **5**, obtained by treatment of **2a** or **2b** with *m*-chloroperbenzoic acid, were also formed as single diastereoisomers. However, exposing **5** to conventional Cope conditions (pyrolysis at 100–150 °C) resulted in the formation of a compound mixture whose separation was not practicable. Fortunately, refluxing **5** in methanolic potassium hydroxide solution afforded a major product which could be isolated in reasonable yield. The $^1H$ NMR spectrum indicated a separated methylene group, with its two additional doublets at $\delta$ 3.95 and 4.26 possessing a typical geminal coupling constant ($J$ 13 Hz), thereby pointing to the structure **7**.[6] Additional evidence was provided by the downfield shift of the *N*-methyl group to $\delta$ 2.61

* A shift of more than 2 Å, compared with morphine, can be deduced from the X-ray analysis of **3**.[2]

and an analogous shift of C-5 in the corresponding $^{13}C$ spectrum, in comparison with the NMR spectral data of **3**. Thus, the reaction conditions employed caused the intramolecular *O*-alkylation and directly furnished the oxazepine **7**. Retrospectively regarded, the *S*-configuration of the starting *N*-oxides **5** can be deduced.

Under the selected Cope conditions, a by-product was isolated and finally identified as **3** (see Scheme 1). While **5a** and **5b** were proved to be free of **2a** (and **2b**, respectively) by NMR spectroscopic analysis, amine **3** could only be formed *via* reduction of **5** under the Cope conditions used. This behaviour could be explained by the known susceptibility of *N*-oxides to reduction.[7] Similar observations have been made on *N*-oxides of 14-methyldihydro-C-nor-codeinones.[5]

The further steps, hydrogenation (→**9**) and acetal cleavage, led to **10** which appears as an *O*-homologue of the leading compound **4** (see Scheme 3). Pharmacological properties of compound **10** (and **8**) are being investigated in on-going studies.




**Scheme 3** *Reagents and conditions:* i, HCl (2 mol $dm^{-3}$); ii, $H_2$, Pd–C, AcOH, 80 °C

## Experimental

M.p.s were determined on a Kofler microscope. IR spectra were recorded on a Perkin-Elmer 298 instrument. $^1H$ and $^{13}C$ NMR spectra were measured with a Bruker AC 80 instrument [$^1H$ NMR: tetramethylsilane as internal standard, *J*-values given in Hz; $^{13}C$ NMR: chemical shifts in ppm relative to the resonance of $CDCl_3$ ($\delta$ 77.0)]. Mass spectra were determined on a Finnigan MAT 111A. Chromatographic separations were carried out as preparative TLC on aluminium oxide plates.

Starting 14-halogenomethyl-C-nor-dihydrocodeinone acetals were prepared according to ref. 1.

(5R,9R,13R,14S,17S)-14-*Chloromethyl*-4,5-*epoxy*-3-*methoxy*-17-*methyl*-C-*normorphinan*-6-*one Dimethyl Acetal* N-*Oxide* **5a**.—To a solution of compound **2a** (300 mg, 0.79 mmol) in $CH_2Cl_2$ (10 $cm^3$) was added *m*-chloroperbenzoic acid (87%; 173 mg, 0.87 mmol) and the mixture was stirred for 1 h. Aqueous sodium carbonate (2 mol $dm^{-3}$; 20 $cm^3$) was then added to the mixture after which it was further stirred for 10 min. The organic layer was separated, washed with aqueous sodium hydroxide (2 mol $dm^{-3}$; 2 × 5 $cm^3$), dried ($Na_2SO_4$) and evaporated to afford **5a** as a colourless oil (270 mg, 83%) (Found: C, 57.75; H, 6.6; N, 3.2. $C_{20}H_{26}NO_5Cl{\cdot}H_2O$ requires C, 58.03; H, 6.81; N, 3.38%); $\delta_H(CDCl_3)$ 1.36 (1 H, d, $J_{7a,7b}$ 14, 7a-H), 2.23 (1 H, d, $J_{7a,7b}$ 14, 7b-H), 3.20 and 3.27 (each 3 H, each s, 2 × 6-OMe), 3.90 (3 H, s, 3-OMe), 4.06 (3 H, br s, NMe), 4.67 (1 H and 2 H, br s, 5-H and $H_2O$), 5.47 (1 H, br d, $J_{8a,8b}$ 8, 8a-H), 6.86 (2 H, s, 1- and 2-H); *m/z* 395/397 ($M^+$).

(5R,9R,13R,14S,17S)-14-*Bromomethyl*-4,5-*epoxy*-3-*methoxy*-17-*methyl*-C-*normorphinan*-6-*one Dimethyl Acetal* N-*Oxide* **5b**.—Similarly, compound **2b** (335 mg, 0.79 mmol) gave **5b** as a yellow oil (330 mg, 91%) (Found: C, 52.15; H, 5.9; N, 2.95. $C_{20}H_{26}NO_5Br{\cdot}H_2O$ requires C, 52.41; H, 6.16; N, 3.06%); $\delta_H(CDCl_3)$ 1.00 (1 H, d, $J_{7a,7b}$ 14, 7a-H), 1.77 (1 H, d, $J_{7a,7b}$ 14, 7b-H), 3.24 (6 H, s, 2 × 6-OMe), 3.79 (3 H, s, NMe), 3.91 (3 H, s, 3-OMe), 4.68 (1 H and 2 H, br s, 5-H and $H_2O$), 5.60 (1 H, br d, $J_{8a,8b}$ 8, 8a-H), 6.59 and 6.89 (2 H, AB-system, $J_{1,2}$ 8, 1- and 2-H); *m/z* 439/441 ($M^+$).

(5aR,11bS,12R)-11,12-*Epoxy*-10-*methoxy*-3-*methyl*-1,2-*dihydro*-3H,5H-5a,11b-*propanonaphtho*[1,2-e][1,2]*oxazepin*-13-*one Dimethyl Actal* **7**.—A solution of compound **5a** (300 mg, 0.76 mmol) in methanolic potassium hydroxide (1 g KOH in 20 $cm^3$ MeOH) was boiled under reflux for 24 h. After dilution with water, the solution was extracted with $CH_2Cl_2$ (3 × 20 $cm^3$). The combined extracts were dried ($Na_2SO_4$), concentrated and chromatographed [light petroleum–ethyl acetate–triethylamine (90:10:5) as eluent] to yield **7** as a colourless oil (160 mg, 61%). Compound **3**, a by-product was also isolated (30 mg). Similarly, compound **5b** (330 mg, 0.76 mmol) also gave compounds **7** (185 mg, 71%) and **3** (20 mg) (Found: C, 66.8; H, 7.0; N, 3.9. $C_{20}H_{25}NO_5$ requires C, 66.84; H, 7.01; N, 3.90%); $\delta_H(CDCl_3)$ 2.61 (3 H, s, NMe), 3.23 (6 H, s, 2 × 13-OMe), 3.86 (3 H, s, 10-OMe), 3.95 (1 H, d, $J_{5a,5b}$ 13, 5a-H), 4.26 (1 H, d, $J_{5a,5b}$ 13, 5b-H), 5.06 (1 H, s, 12-H), 5.51 (1 H, d, $J_{6,7}$ 9.5, 6-H), 6.41 (1 H, d, $J_{6,7}$ 9.5, 7-H), 6.54 and 6.62 (2 H, AB-system, $J_{8,9}$ 8, 8- and 9-H); $\delta_C(CDCl_3)$ 28.4, 29.6, 44.6, 57.1 and 57.9 (C-1, - 2, -5a, -11b and -14), 46.5, 48.8 and 50.4 (NMe and 2 × 13-OMe), 56.4 (10-OMe), 80.4 (C-5), 92.2 (C-12), 109.2 (C-13), 113.0 (C-9), 117.4 (C-8), 124.6 (C-6), 135.2 (C-7), 109.2, 115.1, 133.5 and 139.6 (C-7a, -10, -11 and -11a); *m/z* 359 ($M^+$).

(5aR,11bS,12R)-11,12-*Epoxy*-10-*methoxy*-3-*methyl*-1,2-*dihydro*-3H,5H-5a,11b-*propanonaphtho*[1,2-e][1,2]*oxazepin*-13-*one* **8**.—A solution of compound **7** (360 mg, 1 mmol) in hydrochloric acid (2 mol $dm^{-3}$; 10 $cm^3$) was heated on a water-bath for 10 min after which it was basified with aqueous sodium hydroxide (2 mol $dm^{-3}$) to pH 8 and extracted with $CH_2Cl_2$ (3 × 20 $cm^3$). The combined extracts were dried ($Na_2SO_4$) and then concentrated under reduced pressure to afford **8** as colourless crystals, m.p. 134–135 °C (methanol) (Found: C, 68.75; H, 6.05; N, 4.45. $C_{18}H_{19}NO_4$ requires C, 68.99; H, 6.11; N, 4.47%); $\nu_{max}$(KBr)/$cm^{-1}$ 1750 (C=O); $\delta_H(CDCl_3)$ 2.61 (3 H, s, NMe), 3.87 (3 H, s, OMe), 3.96 (1 H, d, $J_{5a,5b}$ 13, 5a-H), 4.25 (1 H, d, $J_{5a,5b}$ 13, 5b-H), 4.98 (1 H, s, 12-H), 5.68 (1 H, d, $J_{6,7}$ 9, 6-H), 6.55 (1 H, d, $J_{6,7}$ 9, 7-H), 6.68 (2 H, s, 8- and 9-H); *m/z* 313 ($M^+$).

(5aR,11bS,12R)-11,12-*Epoxy*-10-*methoxy*-3-*methyl*-1,2,6,7-*tetrahydro*-3H,5H-5a,11b-*propanonaphtho*[1,2-e][1,2]*oxazepin*-13-*one Dimethyl Acetal* **9**.—A solution of compound **7** (360 mg, 1 mmol) in AcOH (20 $cm^3$) was stirred with 5% palladium on charcoal (40 mg) under an atmosphere of hydrogen for 6 h at 80 °C. The catalyst was filtered off, and the filtrate was evaporated under reduced pressure to afford an oily residue. This was dissolved in water and the solution basified with aqueous sodium carbonate to pH 8 and then extracted with $CH_2Cl_2$ (3 × 10 $cm^3$). The combined extracts were dried ($Na_2SO_4$) and concentrated under reduced pressure to give **9** as a colourless oil (325 mg, 90%) (Found: C, 66.3; H, 7.5; N, 3.9. $C_{20}H_{27}NO_5$ requires C, 66.46; H, 7.53; N, 3.88%); $\delta_H(CDCl_3)$ 2.60 (3 H, s, NMe), 3.20, 3.23 (each 3 H, each s, 2 × 13-OMe), 3.85 (3 H, s, 10-OMe), 3.93 (1 H, d, $J_{5a,5b}$ 13, 5a-H), 4.22 (1 H, d, $J_{5a,5b}$ 13, 5b-H), 5.01 (1 H, s, 12-H), 6.54 and 6.66 (2 H, AB-system, $J_{8,9}$ 8, 8- and 9-H); *m/z* 361 ($M^+$).

(5aR,11bS,12R)-11,12-*Epoxy*-10-*methoxy*-3-*methyl*-1,2,6,7-*tetrahydro*-3H,5H-5a,11b-*propanonaphtho*[1,2-e][1,2]*oxazepin*-13-*one* **10**.—The acetal **9** was hydrolysed as described above for the formation of **8** to afford **10** (290 mg, 92%) as colourless crystals, m.p. 137–138 °C (methanol) (Found: C, 68.4; H, 6.65; N, 4.4. $C_{18}H_{21}NO_4$ requires C, 68.55; H, 6.71; N, 4.44%); $\nu_{max}$(KBr)/cm$^{-1}$ 1745 (C=O); $\delta_H$($CDCl_3$) 2.58 (3 H, s, NMe), 3.82 (3 H, s, OMe), 3.90 (1 H, d, $J_{5a,5b}$ 13, 5a-H), 4.22 (1 H, d, $J_{5a,5b}$ 13, 5b-H), 4.95 (1 H, s, 12-H), 6.56 and 6.66 (2 H, AB-system, $J_{8,9}$ 8, 8- and 9-H); *m*/*z* 315 ($M^+$).

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