# Beckmann Rearrangement of (+)-3-Methoxy-17-methylmorphinan-10-one Oxime



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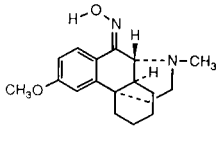
(+)-6,7,7a,8,9,10,11,11a-Octahydro-2-methoxy-12-methyl-5*H*-7,11a-iminoethanodibenz[*c*,*e*]azepin-5-one (**3**) was prepared by Beckmann rearrangement of the oxime of (+)-3-methoxy-17-methylmorphinan-10-one (**2**) with polyphosphoric acid.

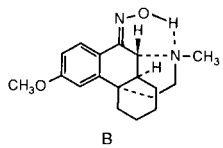
*J. Heterocyclic Chem.*, **23**, 1897 (1986).

A recent publication by Kanematsu *et. al.* [1] on the Beckmann rearrangement of 3,4-dimethoxy-6-morphinanone oxime prompted us to report our own observation in a related area. In this paper, we report, as part of our continuing interest in modifications of the morphinan skeleton [2], the Beckmann rearrangement of the oxime of (+)-3-methoxy-17-methylmorphinan-10-one (**2**).

As shown in Scheme I, reaction of the oxomorphinan **1** [3] with hydroxylamine hydrochloride in pyridine gave the hydrochloride of the oxime **2**, which on treatment with 2*N* sodium hydroxide afforded the corresponding base **2**. Rearrangement of the oxime **2** was accomplished by the use of polyphosphoric acid [4] and from this reaction, we obtained a single lactam to which structure **3** was assigned on the basis of spectral evidence. The uv spectrum (*vide infra*) reflected the influence of the amide carbonyl on the methoxyphenyl chromophore. The ir spectrum had an amide carbonyl bond at 1627 $cm^{-1}$ and the expected NH absorption. The nmr spectrum was in complete agreement with structure **3**. In particular, the signal of one low-field aromatic proton was at $\delta$ 8.57 indicating that it was *ortho* to the carbonyl group. A doublet of doublets at $\delta$ 4.02, collapsable to a simple doublet upon deuterium oxide addition, ($J_{CH\text{-}CH}$ = 6.5 and $J_{CH\text{-}NH}$ = 5 Hz) confirmed the presence of a CH-NH group in the molecule. This feature distinguishes structure **3** from the isomeric lactam **4**.



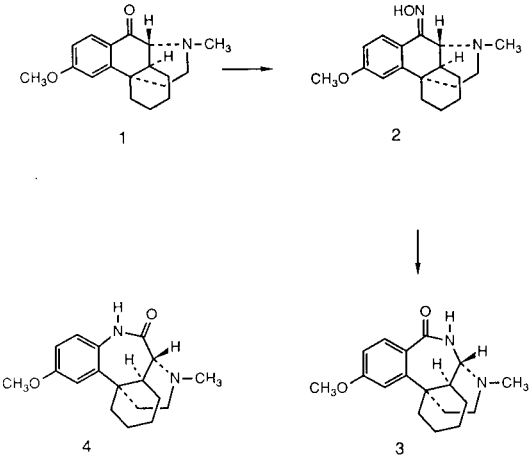
A



B

The relationship between the stereochemistry of the oxime **2** and the stereostructure of the amide **3** was also investigated by spectral data. Since the Beckmann rearrangement is stereospecific [5] the configuration of the oxime **2** may be determined from the structure of the amide **3**, provided that the configuration of **2** is not affected during the reaction. Two isomers A (*syn*) and B (*anti*), are possible for **2**.

Scheme I



1 2 4 3

The nmr spectrum of **2** is compatible with structure A, showing in particular a doublet at $\delta$ 4.30 ($J_{CH\text{-}CH}$ = 3.0 Hz) for $=CH\text{-}N(CH_3)$- proton, a broad singlet at 7.55 for the =N-OH proton and a multiplet centered at 7.30 for the aromatic protons. The assigned stereochemistry is also supported by infrared absorption at 3580 $cm^{-1}$ for a 0.065% solution of **2** in carbon tetrachloride, which is characteristic of a free hydroxyl group. In particular, one may rule out the alternative structure B on the basis that in the ir and nmr spectra of **2** intramolecular hydrogen bonding was not observed which would be expected if the oxime configuration were *anti*. The above data suggest that oxime **2** must have the *syn* configuration, which then rearranges stereospecifically with intramolecular alkyl group migration to yield lactam **3**.

## 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 $\delta$ 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.

(+)-3-Methoxy-17-methylmorphinan-10-one Oxime (**2**).

A solution of 28.5 g (0.1 mole) of (+)-3-methoxy-17-methylmorphinan-10-one (**1**) [3] and hydroxylamine hydrochloride (39.4 g, 0.6 mole) in pyridine (700 ml) was stirred under nitrogen at room temperature for 20 hours then at reflux for 48 hours. The cooled mixture was concentrated under reduced pressure and the crystalline hydrochloride was collected by filtration and washed with water (400 ml). It was recrystallized from methanol to yield 28.8 g (87%) of (+)-3-methoxy-17-methylmorphinan-10-one oxime hydrochloride (**2**), mp 260° dec.

The above hydrochloride of **2**, (21.1 g, 0.06 mole) was added under nitrogen to 2*N* sodium hydroxide (500 ml) and the mixture was stirred on the steam-bath for 2.5 hours. After cooling the crude base **2** was collected by filtration, washed with water (300 ml) and dried. Recrystallization of the crude base from methanol gave 15.5 g (82%) of (+)-3-methoxy-17-methylmorphinan-10-one oxime (**2**), mp 216-217°; $[\alpha]_D^{25}$ -99.81° (c = 1.1, methanol); ir (chloroform): 3580 $cm^{-1}$ (=N-OH); uv (95% ethanol): max 268 m$\mu$ ($\epsilon$ 15350), infl 294 (5700) and infl 305 (3500); ms: m/e 300 [M$^+$]; nmr (deuteriochloroform): $\delta$ 7.55 (s, 1H, =N-OH), 7.30 (m, 3H, ArH), 4.30 (d, 1H, $J_{CH-CH}$ = 3.0 Hz, CHN), 3.82 (s, 3H, $OCH_3$) and 2.39 (s, 3H, $NCH_3$).

*Anal.* Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.14; H, 8.25; N, 9.51.

(+)-6,7,7a,8,9,10,11,11a-Octahydro-2-methoxy-12-methyl-5*H*-7a,11a-iminoethanodibenz[*c,e*]azepin-5-one (**3**).

A stirred mixture of 13.2 g (0.04 mole) of (+)-3-methoxy-17-methylmorphinan-10-one oxime (**2**) and polyphosphonic acid (300 g) was heated under nitrogen in an oil bath, maintained at 100° for 1 hour. The reaction mixture was cooled and poured into a mixture of ice and water (500 ml). The polyphosphoric acid was hydrolyzed and the mixture made basic with concentrated ammonium hydroxide. The aqueous suspension was extracted with chloroform (3 x 300 ml). The organic solutions were combined, washed with brine then dried (magnesium sulfate) and removal of the solvent gave a brown residue which was chromatographed on silica gel to yield 7.3 g (55%) of (+)-6,7,7a,8,9,10,11,11a-octahydro-2-methoxy-12-methyl-5*H*-7a,11a-iminoethanodibenz[*c,e*]azepin-5-one (**3**), mp 199-200°; $[\alpha]_D^{25}$ +204.54° (C = 1.17, methanol); ir (chloroform): 3550 (NH) and 1627 $cm^{-1}$ (C=O); uv (95% ethanol): max 212 m$\mu$ ($\epsilon$ 29100) and 258 (12350); nmr (deuteriochloroform): $\delta$ 8.57 (d, 1H, $J_{ortho}$ = 9.0 Hz, ArH) and 4.02 (dd, 1H, $J_{CH-CH}$ = 6.5 Hz and $J_{CH-NH}$ = 5.0 Hz, deuterium oxide collapsable to doublet); ms: m/e 300 [M$^+$].

*Anal.* Calcd. for $C_{18}H_{24}N_2O_2$: C, 71.97; H, 8.05; N, 9.33. Found: C, 72.14; H, 7.98; N, 9.38.

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