

STEREOSELECTIVE FORMAL SYNTHESIS OF (+)-MONOMORINE I FROM
6-METHYL-2-PIPERIDINONE

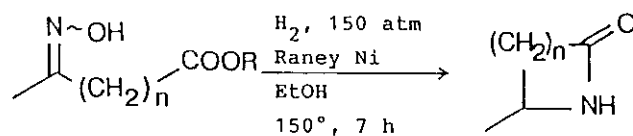
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Abstract — The stereoselective formal synthesis of (+)-monomorphine I from 6-methyl-2-piperidinone was achieved. A general method for the synthesis of ω -alkylated lactams is also described.

The *N*-alkoxycarbonylation of a lactam was found to activate the carbonyl group of the lactam to make it more reactive to nucleophiles such as hydrides¹ and carbanions.² Some antibiotics,³ alkaloids,⁴ and metabolites⁵ have been synthesized by this means. In the present study, the stereoselective formal synthesis of (+)-monomorphine I (**13**) from 6-methyl-2-piperidinone (**7**) is described. (+)-Monomorphine I is an alkaloid isolated from the cosmopolitan ant, *Monomorium pharaonis* (L.).⁶ Although it was possible to obtain 6-methyl-2-piperidinone (**7**) by the Schmidt reaction of 2-methylpentanone⁷ or the Grignard reaction of glutarimide followed by reduction with sodium cyanoborohydride,⁸ these methods are not convenient and their yields are not reproducible.⁸ Thus, a general method for the preparation of ω -methyl lactams was devised and is shown in Scheme 1. Reductive cyclization (H_2 , 150 atm, Raney Ni, 150°C, 7 h) of oximes (**2-4**)⁹ gave ω -methyl lactams (**6-8**) in

Scheme 1



1: n=1, R=Me

2: n=2, R=Me

3: n=3, R=Et

4: n=4, R=Me

5: n=1 0%

6: n=2 70%

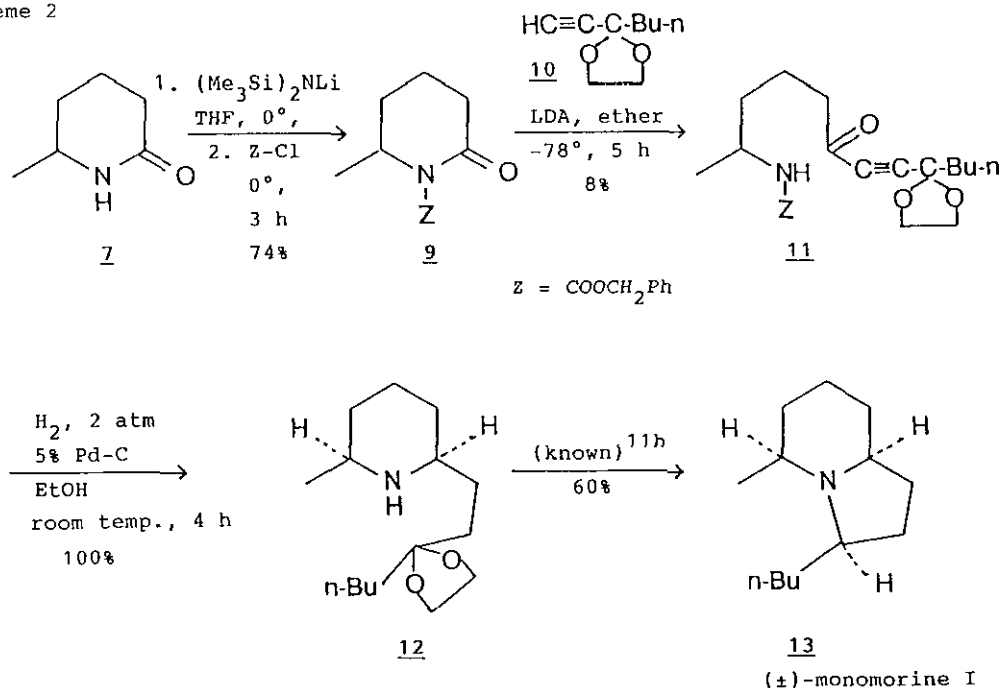
7: n=3 100%

8: n=4 59%

good yields. This method is thus shown to be effective for the synthesis of ω -alkylated five to seven membered lactams, though the β -lactam (5) could not be obtained under the similar conditions.

The synthesis of ($\pm$)-monomorine I (13)¹⁰ using 6-methyl-2-piperidinone (7) was subsequently carried out according to the method presented in Scheme 2. Reaction of 7 with benzyl chloroformate in the presence of lithium bis(trimethylsilyl)-amide gave N-benzyloxycarbonyllactam (9) in 74% yield. The ring opening reaction of 9 with the acetylene (10)^{10h} was carried out diligently and carefully by the method reported by Nozoe and co-workers^{2,3} to give the desired product (11) but only in low yield (8%).¹¹ The reactivity of the six membered lactam appeared to differ from that of the five membered lactam. The catalytic hydrogenation of 11 over 5% palladium-carbon gave the known cis-1,6-disubstituted piperidine (12)^{10h} in quantitative yield. No trans-isomer could be detected by its nuclear magnetic resonance spectrum and thin layer chromatography. The spectral data of 12 synthesized in this study showed complete agreement with those of an authentic sample as reported in the literature.^{10h} The stereoselective synthesis of ($\pm$)-monomorine I (13) from 12 is known^{10h} and so the formal synthesis of 13 was possible here.

Scheme 2



EXPERIMENTAL

All melting points were determined by micro-melting point apparatus (Yanagimoto) without correction. Ir and mass spectra were measured on a Hitachi 200-10 spectrophotometer and a Hitachi M-80 spectrometer, respectively. ^1H - and ^{13}C -Nmr spectra were recorded on Varian EM-390 and/or Bruker M-400 instruments. Chemical shifts were recorded in ppm downfield from an internal standard (tetramethylsilane). Thin layer chromatography (tlc) was carried out with precoated silica gel plates (Kiesel 60 F-254, Merck).

General Procedure for Preparation of ω -Methylactams (6, 7, 8) -- A typical procedure is described for 6-methyl-2-piperidinone (7): A mixture of 3 (9.62 g, 56 mmol) and Raney Ni (ca. 2 g) in EtOH (100 ml) was subjected to catalytic hydrogenation at 150°C for 7 h under 150 atm of hydrogen pressure, then allowed to cool. The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to give a solid which, on recrystallization from hexane, gave 6.28 g (100%) of pure 7 as colorless prisms, mp $87-88^\circ\text{C}$ (lit.⁷ mp $87-88^\circ\text{C}$). Ir (CHCl_3) 3430, 1685 cm^{-1} . ^1H -Nmr (CDCl_3) δ 1.15 (3H, d, $J=7\text{Hz}$, Me), 1.30-2.00 (4H, m, $\text{CH}_2 \times 2$), 2.15-2.40 (2H, m, CH_2CO), 3.25-3.65 (1H, m, CH), 6.10 (1H, br, NH). Ms m/z 113 (M^+).

6: mp $41-43^\circ\text{C}$. This compound is commercial available (Tokyo Kasei Kogyo Co.). ^1H -Nmr (CDCl_3) δ 1.21 (3H, d, $J=7\text{Hz}$, Me), 1.40-2.50 (4H, m, $\text{CH}_2 \times 2$), 3.60-3.90 (1H, m, CH), 7.10 (1H, br, NH).

8: mp $91-92^\circ\text{C}$ (lit.¹² mp $90.5-91.5^\circ\text{C}$). Ir (CHCl_3) 3430, 1685 cm^{-1} . ^1H -Nmr (CDCl_3) δ 1.20 (3H, d, $J=7\text{Hz}$, Me), 1.30-2.10 (6H, m, $\text{CH}_2 \times 3$), 2.20-2.50 (2H, m, CH_2CO), 3.30-3.65 (1H, m, CH), 5.90 (1H, br, NH). Ms m/z 127 (M^+).

1-Benzoyloxycarbonyl-6-methyl-2-piperidinone (9) -- A solution of $(\text{Me}_3\text{Si})_2\text{NLi}$ (4.4 mmol) in hexane was added at 0°C to a solution of 7 (452 mg, 4 mmol) in THF (20 ml) under an argon atmosphere followed by stirring at the same temperature for 30 min. A solution of $\text{ClCOOCH}_2\text{Ph}$ (4.1 mmol) in toluene (2.4 ml) was added dropwise to the above solution with stirring at 0°C over a period of 30 min. After being stirred at 0°C for 3 h, the reaction mixture was neutralized with an aqueous NH_4Cl solution, diluted with H_2O , and then extracted with Et_2O several times. The extract was washed with brine, dried over MgSO_4 , and evaporated to give an oil (1.6 g) which, on chromatographic separation (silica gel) by elution with hexane-acetone (15:1), gave 731 mg (74%) of 9 as a colorless oil, bp 190°C (4 mmHg). Ir

(neat) 2950, 1765, 1710 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ 1.20 (3H, d, $J=7\text{Hz}$, Me), 1.50- 2.10 (4H, m, $\text{CH}_2 \times 2$), 2.40-2.60 (2H, m, CH_2), 4.40 (1H, br, CH), 5.30 (2H, s, CH_2), 7.37 (5H, s, Ph). Ms m/z 247 (M^+). Anal. Calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_3$: C, 67.99; H, 6.93; N, 5.66. Found: C, 67.58; H, 7.02; N, 5.63.

2-Carbobenzyloxyamino-9-ethylenedioxy-7-tridecyn-6-one (11) -- A solution of *n*-BuLi (2.5 mmol) in hexane was added at -78°C to a solution of diisopropylamine (404 mg, 4 mmol) in Et_2O (10 ml) under an argon atmosphere. This was followed 15 min later by the addition of a solution of 10^{10h} (400 mg, 2.6 mmol) in Et_2O (1 ml) and stirring at -78°C for 30 min. A solution of 9 (500 mg, 2 mmol) in Et_2O (1 ml) was then added dropwise and the reaction mixture was stirred at -78°C for 5 h. Neutralization was effected by adding an aqueous NH_4Cl solution, followed by extraction with Et_2O . The extract was washed with brine, dried over MgSO_4 , and evaporated. Chromatographic separation on silica gel by elution with hexane-acetone (10:1) gave 64 mg (8%) of 11 as a colorless oil. Ir (CHCl_3) 3440, 2955, 2400, 1710, 1675, 1510 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ 0.90 (3H, t, $J=7\text{Hz}$, Me), 1.10 (3H, d, $J=7\text{Hz}$, Me), 1.10-2.00 (10H, m, $\text{CH}_2 \times 5$), 2.57 (2H, t, $J=7\text{Hz}$, CH_2CO), 3.52-3.90 (1H, m, NCH), 3.90-4.10 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$), 5.06 (2H, t, CH_2Ph), 7.33 (5H, s, Ph). Ms (CI) m/z (rel intensity) 402 ($\text{M}^+ + 1$, 0.4), 358 (3), 344 (1), 295 (44), 236 (38), 129 (100). High resolution ms Calcd for $\text{C}_{19}\text{H}_{22}\text{NO}_5$ ($\text{M}^+ - \text{Bu}$): 344.1497. Found: 344.1527.

cis-2-(3,3-Ethylenedioxyheptyl)-6-methylpiperidine (12) -- A mixture of 11 (63 mg, 0.157 mmol) and 5% Pd-C (50 mg) in EtOH (5 ml) was subjected to catalytic hydrogenation at room temperature for 3 h under 2 atm of hydrogen pressure. The catalyst was removed by filtration and the filtrate was concentrated to give a yellow oil which, on chromatographic separation on alumina by elution with CHCl_3 , gave 40 mg (100%) of 12 as a yellow oil. Ir (CHCl_3) 3350, 1460, 1100 cm^{-1} . $^1\text{H-Nmr}$ (CDCl_3) δ 0.89 (3H, t, $J=7\text{Hz}$, Me), 1.05 (3H, t, $J=7\text{Hz}$, Me), 1.10-1.90 (17H, m, $\text{CH}_2 \times 8$, NH), 2.30-2.80 (2H, m, NCH $\times$ 2), 3.92 (4H, m, $\text{OCH}_2\text{CH}_2\text{O}$). $^{13}\text{C-Nmr}$ (CDCl_3) δ 111.8, 64.9, 57.5, 52.6, 37.0, 34.4, 33.6, 32.2, 31.6, 26.0, 24.9, 23.1, 23.0, 14.0. Ms m/z 255 (M^+).

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9. Oximes (1-4) were prepared by reactions of oxo-esters with hydroxylamine under neutral or acidic conditions.
- 1 (oil): $^1\text{H-Nmr}$ (CDCl_3) δ 1.95 (3H, s, Me), 3.20 (2H, s, CH_2), 3.65 (3H, s, OMe), 9.20 (1H, br, OH).
- 2 (mp 44-45°C): $^1\text{H-Nmr}$ (CDCl_3) δ 1.87 (3H, s, Me), 2.48-2.77 (4H, m, $\text{CH}_2 \times 2$), 3.65 (3H, s, OMe), 8.50 (1H, br, OH).
- 3 (oil): $^1\text{H-Nmr}$ (CDCl_3) δ 1.20 (3H, t, $J=7\text{Hz}$, Me), 1.70-2.40 (6H, m, $\text{CH}_2 \times 3$), 2.00 (3H, s, MeC=N), 4.13 (2H, q, $J=7\text{Hz}$, CH_2Me), 8.50 (1H, br, OH).
- 4 (oil): $^1\text{H-Nmr}$ (CDCl_3) δ 1.50-1.87 (4H, m, $\text{CH}_2 \times 2$), 1.87 (3H, s, Me), 2.13-2.57 (4H, m, $\text{CH}_2 \times 2$), 3.67 (3H, s, OMe).
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11. Various reaction conditions [Base: n-BuLi, LDA, (Me₃Si)₂NLi, CeCl₃-LDA, NaH, KOH. Solvent: ether, THF, C₆H₆. Temperature: from -78°C to room temp.] were examined.
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