BECKMANN REARRANGEMENT OF 3,4-DIMETHOXY-6-MORPHINANONE OXIME

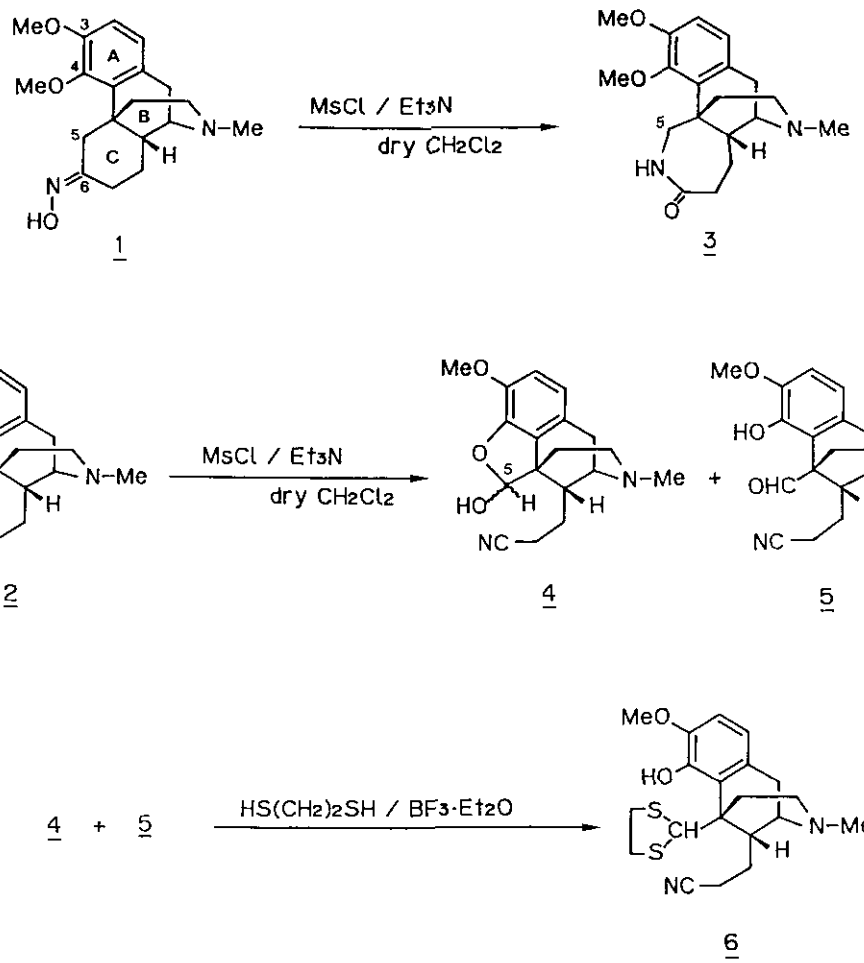
Ikuo Fujii, Michiko Irie, Kenji Hayakawa, and Ken Kanematsu*
Institute of Synthetic Organic Chemistry, Faculty of Pharmaceutical Sciences, Kyushu University 62, Fukuoka 812, Japan

Abstract - The Beckmann rearrangememts under neutral conditions of 3,4-dimethoxy-6-morphinanone oxime (1) and dihydrocodeinone oxime (2) proceed very smoothly but in the different ways to provide lactam (3) and hemiacetal (4), respectively.

Ring enlargement reactions of morphine alkaloids would give a new class of compounds with the novel ring systems.[1,2] While the Beckmann rearrangements of ketoximes under acidic conditions usually give amides, dihydrocodeinone oxime (2) was reported to undergo the abnormal cleavage of ring C affording nitrile (5),[3] due to the participation of the neighbouring oxygen atom at C-5.[4] This prompted us to reinvestigate the same reaction using the substrates without the 4,5-ether bridge.

We wish to report here the successful C-ring expansion of 3,4-dimethoxy-6-morphinanone oxime (1) to produce lactam (3) by the Beckmann rearrangement under almost neutral reaction conditions. To our best knowledge, this is a first example of ring enlargement of a morphine derivative by Beckmann rearrangement.

Treatment of the oxime (1), prepared from dihydrocodeinone[5] with methanesulphonyl chloride (1.2 equiv.) in the presence of triethylamine (1.5 equiv.) in dry CH_2Cl_2 at 0°C (30 min.) followed by quenching with water, gave the crystalline product (3), mp 187-190°C, as the sole product in 57% yield. The structure of compound (3) was determined on the basis of its spectroscopic data. The nature as an amide was apparent from ir spectrum which showed a characteristic absorption at



1660 cm^{-1}. The regiochemistry of the rearrangement product was clearly revealed by the ^{1}H-nmr spectrum. The most diagnostic features were the signals of the methylene protons adjacent to the lactam nitrogen atom which appeared at δ 3.31 and 3.89 as the ABX-pattern (J = 15, 7 Hz). In the decoupling experiments, irradiation of the NH signal (δ 6.01) or even D_2O-addition (25°C, 20 h) caused the simplification of their signals to the AB-pattern. The ^{13}C-nmr spectrum showed a signal of amide carbonyl (δ 176.8, s).

In order to study the effects of the ring oxygen at C-5, the Beckmann rearrangement of the oxime (2) under the similar reaction condition was also examined. When (2) was treated with methanesulphonyl chloride and triethylamine at 0°C, a smooth reaction occurred to give a mixture of two products in a quantitative yield which were separated carefully by flash column chromatogrophy. Interestingly, from less polar fractions the hemiacetal (4), mp 125°C, was isolated for the first time in 60% yield, whereas the known nitrile (5)[3] was isolated (36%) from more polar fractions. The structure of compound (4) was confirmed by its spectroscopic data and chemical conversions. In the ^{1}H-nmr spectrum, compound (4) showed singlets for H-5 and alcohol at δ 6.24 and 3.60, respectively. No absorption band for aldehyde was observed by the IR spectrum. The hemiacetal (4) was slowly converted to the nitrile (5) on standing at room temperature, and treatment of the mixture of 4 and 5 with ethylene dithiol in the presence of $BF_3 \cdot Et_2O$ produced the thioacetal (6), mp 87-90°C, in 73 % yield.
The above results clearly indicate the important role of the 4,5-ether bridge affecting the reaction course in the Beckmann rearrangements of the morphine derivatives.

EXPERIMENTAL

Melting points were measured with a Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra were recorded on a JASCO IR A-100 spectrophotometer. ^{1}H- and ^{13}C- nmr spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standerd on a JEOL PS-100 spectrometer and a JEOL FX-100 spectrometer, respectively. Mass spectra were determined on a JEOL D-300 equipped with JMS 3100/3500 at an ionization voltage of 30 eV.

Preparation of 3,4-dimethoxy-6-morphinanone oxime (1)

A solution of 600 mg (1.90 mmol) of 3,4-dimethoxy-6-morphinanone[5], hydroxylamine hydrochloride (264 mg, 3.80 mmol) and sodium acetate (777 mg, 5.71 mmol) in ethanol (45 ml) - H_2O (13 ml) was refluxed for 1 h. The solvent was removed in vacuo, then the residue was extracted with chloroform. The organic layer was dried and concentrated in vacuo to give crude product which was recrystallized from ethanol to yield pure oxime 1 (446 mg, 71 %) as white crystals: mp 210-213°C; ir ($CHCl_3$) 3300 cm^{-1}; ^{1}H nmr δ 1.40-2.12 (m, 8H), 2.34-2.57 (m, 1H), 2.36 (s, 3H, NMe), 2.68-3.33 (m, 4H), 3.76 (s, 3H, OMe), 3.88 (s, 3H, OMe), 3.90 (d, J

= 14 Hz, 1H), 6.63 (s, 2H, ArH), 9.28 (br s, 1H, NOH, D_2O disappear); ms m/z 330 [M^+]; $[\alpha]_D^{25°}$ +12.9°(c = 2.0, $CHCl_3$); Anal. Calcd. for $C_{19}H_{26}O_3N_2$: C, 69.09; H, 7.88; N, 8.48. Found: C, 68.70; H, 7.87; N, 8.38.

Beckmann rearrangement of 3,4-dimethoxy-6-morphinanone oxime (1)

To a suspension of 1 (185 mg, 0.56 mmol) and triethylamine (85 mg, 0.84 mmol) in dry CH_2Cl_2 (20 ml) was added 76 mg (0.67 mmol) of methanesulphonyl chloride at 0°C under Ar. The TLC analysis showed that the reaction was completed in 30 min. The resulting mixture was poured on ice-water, rendered alkaline with 30 % NH_4OH-solution and extracted with chloroform. The organic layer was dried and evaporated in vacuo to give a brown residue which was chromatographed on silica gel to yield lactam 3 (106 mg, 57 %) as a white solid: mp 187-190°C; ir ($CHCl_3$) 1660 cm^{-1}; ^1H nmr δ 1.00-2.40 (m, 9H), 2.48 (s, 3H, NMe), 2.60-3.08 (m, 3H), 3.31 (dd, J = 15 and 7 Hz, 1H, H-5), 3.73 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.89 (dd, J = 15 and 7 Hz, 1H, H-5), 6.01 (br t, J = 7 Hz, 1H, NH, D_2O disappear), 6.75 (s, 2H, ArH); ^{13}C nmr δ 23.8 (t), 24.9 (t), 35.4 (t), 35.9 (t), 39.7 (s), 41.7 (q), 47.0 (t), 49.6 (q), 51.3 (t), 55.8 (q), 59.1 (d), 60.4 (d), 111.9 (d), 123.7 (d), 128.8 (s), 129.2 (s), 147.5 (s), 151.3 (s), 176.8 (s); ms m/z 330 [M^+]; $[\alpha]_D^{25°}$ -6.72°(c = 1.25, $CHCl_3$); Anal. Calcd. for $C_{19}H_{26}O_3N_2 \cdot 2H_2O$: C, 62.30; H,7.10; N, 7.65. Found: C, 62.44; H, 7.45; N, 7.19.

Beckmann rearrangement of dihydrocodeinone oxime (2)

To a suspension of 2 (1.85 g, 5.87 mmol) and triethylamine (890 mg, 8.80 mmol) in dry CH_2Cl_2 (140 ml) was added 802 mg (7.04 mmol) of methanesulphonyl chloride at 0°C under Ar. The reaction was completed in 30 min. The resulting mixture was poured on ice-water, rendered alkaline with 30 % NH_4OH-solution and extracted with chloroform. The organic layer was dried and evaporated in vacuo to give a brown residue. The flash chromatography ($CHCl_3$: MeOH = 20 : 1) on silica gel provided hemiacetal 4 (1.11 g, 60 %) as a white solid from less polar fractions and nitrile 5 (0.67 g, 36 %) as a white solid from more polar fractions.

4; mp 125°C; ir ($CHCl_3$) 2250 cm^{-1}; ^1H nmr δ 1.40-1.82 (m, 3H), 2.08-2.70 (m, 7H), 2.42 (s, 3H, NMe), 3.04 (d, J = 18 Hz, 1H), 3.22 (dd, J = 6 and 2 Hz, 1H), 3.60 (br s, 1H, OH, D_2O disappear), 3.85 (s, 3H, OMe), 6.24 (s, 1H, H-5), 6.72 and 6.78 (ABq, J = 8 Hz, 2H, ArH):

5; mp 207-208°C; ir ($CHCL_3$) 3540, 2280, 1730 cm^{-1}; ^1H nmr δ 1.60-2.83 (m, 10H),

2.44 (s, 3H, NMe), 2.97-3.20 (m, 2H), 3.86 (s, 3H OMe), 5.32 (br s, 1H, ArOH, D_2O disappear), 6.74 and 6.76 (ABq, J = 8 Hz, 2H, ArH), 9.67 (s, 1H, CHO); ms m/z 314 [M^+]; $[\alpha]_D^{25°}$ -82.5°(c = 2.0, $CHCl_3$).

Thioacetalization of hemiacetal (4) and nitril (5)

To a solution of the mixture (185 mg, 0.59 mmol) of 4 and 5 in ethanedithiol (0.2 ml), 0.1 ml of boron trifluoride etherate was added, then stirred for 2.5 h at room temperature. The resulting mixture was poured on ice-water, rendered alkaline with sat. $NaHCO_3$-solution and extracted with chloroform. The organic layer was dried and evaporated in vacuo to give a brown residue which was chromatographed on silica gel to yield thioacetal 6 (168 mg, 73 %) as a pale yellow solid: mp 87-90°C; ir ($CHCl_3$) 3500, 2240 cm^{-1}; ^1H nmr δ 1.40-2.24 (m, 5H) 2.40 (s, 3H, NMe), 2.46-2.78 (m, 4H), 2.80-3.08 (m, 3H), 3.14-3.44 (m, 4H), 3.84 (s, 3H, OMe), 6.10 (s, 1H, H-5), 6.39 (s, 1H, ArOH, D_2O disapppear), 6.67 and 6.70 (ABq, J = 8 Hz, 2H, ArH); ms m/e 390 [M^+]; $[\alpha]_D^{25°}$ +40.0°(c = 2.0, $CHCl_3$); Anal. Calcd. for $C_{20}H_{26}O_2N_2S_2$ H_2O: C, 58.82; H, 6.37; N, 6.86. Found: C, 58.14; H, 6.56; N, 6.30.

ACKNOWLEDGEMENT

We thank Ms. Noriko Akagi for her technical assistance.

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Received, 11th July, 1985