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Synthesis of 1,3-Bridged 1,2,3,4,5,6-Hexahydro-2,6-methano-3-benzazocine Derivatives[1]

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Two 1,3-bridged 1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine derivatives (**1** and **2**) have been synthesized starting from 3,6-dimethyl-8-methoxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine **3** as shown in Chart 1. Compounds **1** and **2** showed no significant analgesic activity.

Keywords——1,3-bridged 6,7-benzomorphan; analgesic activity; carbethoxymethylation of ketone; lactam; amino ester; stereospecific reduction of olefin; $LiAlH_4$; $NaBH_4$

There has recently been much interest in the synthesis and properties of potential analgesics having a simplified morphine ring system. Chemical modifications by altering the substituents at several positions of 6,7-benzomorphan have been intensively studied, and these modifications have produced a considerable number of compounds possessing various profiles of narcotic antagonist and analgesic activities.[3] Analgesic activity has also been found in a number of homologs of 6,7-benzomorphan including the B-nor,[4] C-nor-,[5] C-homo-[5] and B-nor-C-homobenzomorphan systems.[6] In order to investigate further the structure-activity relationships in benzomorphan and its homologs, we decided to introduce another bridging group connecting the nitrogen atom and the benzylic carbon of benzomorphan and its homologs. This modification creates a very rigid bridged tetracyclic ring system and should affect the steric environment around the nitrogen and above the aromatic ring. Several workers have proposed the importance of this steric environment for binding on the receptor site.[7] This modification also fixes the orientation of the N-lone electron pair away from the

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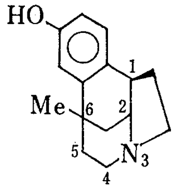
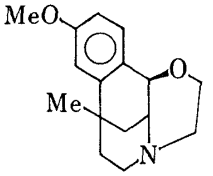
aromatic ring. Belleau *et al.* have postulated the importance of the orientation of the N-lone electron pair for interaction with the opiate receptor.[8] Snyder *et al.* have proposed that the conformation of the N-substituents determines the "purity" of antagonist properties of the drug.[9]

In this paper, the synthesis of 8-hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-1,3-ethano-2,6-methano-3-benzazocine (**1**) and 8-methoxy-1,2,3,4,5,6-hexahydro-1,3-epoxyethano-2,6-methano-3-benzazocine (**2**) is described, and their analgesic properties are reported.

The synthesis of compounds **1** and **2** is outlined in Chart 1. 3,6-Dimethyl-8-methoxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (**3**)[10] was oxidized with CrO_3 to give the



1



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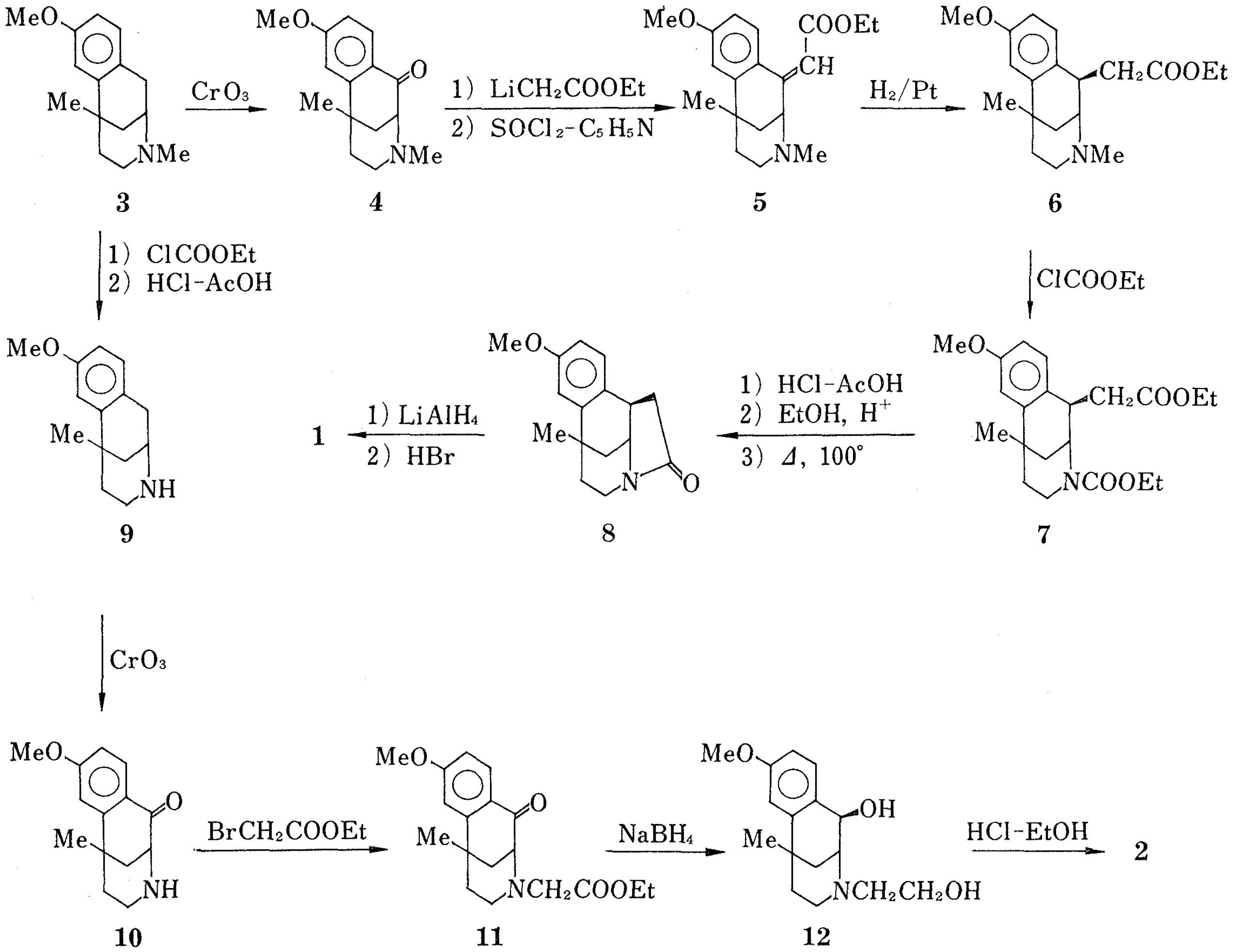

Chart 1

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[8] B. Belleau, T. Conway, F.R. Ahmed, and A.D. Hardy, *J. Med. Chem.*, **17**, 907 (1974).

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ketone **4**, which was treated with $LiCH_2COOEt$, followed by dehydration with $SOCl_2$-pyridine, to give the 1-ethoxycarbonylmethylene compound (**5**) in 68% yield. Hydrogenation of **5** over Pt gave the 1-ethoxycarbonylmethyl derivative (**6**). In the catalytic hydrogenation of **5**, hydrogen should attack from the less hindered side to give 1β-ethoxycarbonylmethyl isomer, and this assumed configuration at C-1 of **6** was established by its cyclization to compound **8**. The amino ester **6** was refluxed with ethyl chloroformate to afford the corresponding urethane (**7**), which was subsequently hydrolyzed to give an amino acid. Esterification of the carboxyl group and cyclization by heating at 100° gave the desired lactam (**8**) in 11% overall yield (from **5**). The lactam **8** was reduced with $LiAlH_4$, followed by O-demethylation with hydrobromic acid to give compound **1** (63% yield from **8**).

Compound **3** was converted to the N-nor derivative (**9**) by refluxing with ethyl chloroformate, and subsequent hydrolysis of the urethane. Oxidation of **9** with CrO_3 gave the ketone **10**, which was treated with ethyl bromoacetate to give the N-ethoxycarbonylmethyl derivative (**11**) in 63% yield. Reduction of **11** with $NaBH_4$ afforded the corresponding diol (**12**). Compound **12** was cyclized by treatment with HCl-ethanol to give the desired 1,3-epoxyethano compound **2** (55% yield from **11**).

Analgesic activities of compounds **1** and **2** were determined by the method of pressure stimuli on the mouse tail after *s.c.* administration.[11] Compounds **1** and **2** showed no significant analgesic activity (morphine, ED_{50} 1.2 mg/kg). Clearly, the introduction of a bridging group between the 1- and 3-position of 6,7-benzomorphan causes almost total loss of analgesic activity.

Experimental

All melting points were determined with a micro melting point apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded on a Hitachi 215 spectrophotometer. NMR spectra were recorded, at 100 MHz, on a JEOL-100 spectrometer with TMS as an internal standard. Mass spectra were recorded on a Hitachi RMU-6MG mass spectrometer. Microanalyses were performed by the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University.

3,6-Dimethyl-8-methoxy-3,4,5,6-tetrahydro-2,6-methano-3-benzazocin-1(2H)-one (4)——A solution of compound 3[10] (5 g, 21.6 mmol) in 1 N H_2SO_4 (80 ml) was mixed with $Na_2Cr_2O_7 \cdot 2H_2O$ (8.5 g, 28.5 mmol) in 1 N H_2SO_4 (80 ml). To this mixture, 10 N H_2SO_4 (330 ml) was added dropwise with stirring during 2 hr at 10—15°. After stirring for 2 days at room temp., the mixture was warmed at 50—60° for 15 min. The ice-cooled mixture was basified with conc. NH_4OH, extracted with ether, and dried (K_2CO_3). Removal of the solvent gave a pale brown oil, which was distilled *in vacuo* to give 4.3 g (81%) of **4** as a pale yellow oil; bp 120—130° (1 mmHg). IR ν_{max}^{film} cm^{-1}: 1675 (Ar–C=O). NMR ($CDCl_3$) δ: 1.41 (3H, s, C_6–Me), 2.29 (3H, s, N–Me), 3.83 (3H, s, O-Me), 6.81 (1H, d, $J=3$ Hz, C_7–H), 6.83 (1H, d–d, $J=3$ Hz, $J'=9$ Hz, C_9–H), 8.01 (1H, d, $J=9$ Hz, C_{10}–H).

1-Ethoxycarbonylmethylene-3,6-dimethyl-8-methoxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (5)——BuLi (7.8 g, 24.5 mmol) in hexane (40 ml) was added to a solution of $(Me_3Si)_2NH$ (4.0 g, 24.5 mmol) in ether (30 ml) over 15 min under N_2 with ice-cooling. After gentle refluxing for 30 min and stirring at room temp., for 1.5 hr, the solvents were evaporated *in vacuo*. The resulting mass was dissolved in dry THF (30 ml) and cooled in a dry ice-acetone bath (−73°). A solution of AcOEt (2.2 g, 24.5 mmol) in dry ether (50 ml) was then added during 30 min. After stirring at this temperature for 30 min, a solution of **4** (2.0 g, 8 mmol) in ether (30 ml) was added during 10 min under N_2 with stirring at −73°; stirring was continued for 3 hr. After addition of H_2O (10 ml), the cold bath was removed. The mixture (at room temp.) was poured into H_2O, extracted with ether and dried ($MgSO_4$). Removal of the solvent gave 2.0 g of a pale yellow syrup, which was used without purification. The residue (2.0 g) was stirred with $SOCl_2$ (20 ml), pyridine (2.0 ml) and $CHCl_3$ (15 ml) at room temp. for 2 hr. The mixture was poured into ice-water, basified with conc. NH_4OH, extracted with ether, and dried (K_2CO_3). Removal of the solvents gave 1.73 g (68%) of **5** has a yellow oil. IR ν_{max}^{film} cm^{-1}: 2790 (N–Me), 1710 (COOEt). NMR ($CDCl_3$) δ: 1.32 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$), 1.40 (3H, s, C_6–Me), 2.34 (3H, s, N–Me), 3.84 (3H, s, O–Me), 4.20 (3H, q, $J=7$ Hz, $COOC\underline{H}_2CH_3$), 5.12—5.26 (1H, m, C_2–H), 6.46 (1H, s, =$C\underline{H}COOEt$), 6.72 (1H, d–d, $J=8$ Hz, $J'=2$ Hz, C_9–H), 6.82 (1H, d, $J=2$ Hz, C_7–H), 7.70 (1H, d, $J=8$ Hz, C_{10}–H). Picrate: mp 146—151° (from MeOH). *Anal.* Calcd for $C_{19}H_{25}O_3 \cdot C_6H_3O_7N_3$: C, 55.15; H, 5.18; N, 10.29. Found: C, 54.86; H, 4.93; N, 10.18.

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6-Methyl-8-methoxy-12-oxo-1,2,3,4,5,6-hexahydro-1,3-ethano-2,6-methano-3-benzazocine (8)——Hydrogenation of **5** (2.1 g, 6.67 mmol) over PtO_2 (0.5 g) in conc. HCl (25 ml) and EtOH (40 ml) at room temp and atmospheric pressure for 20 hr gave compound **6** as a pale yellow oil (2.0 g): IR ν_{max}^{film} cm^{-1}: 1730 (COOEt).

ClCOOEt (2.0 g) in benzene (5 ml) was added to a refluxing solution of **6** (2.0 g) in benzene (50 ml) during 10 min. After refluxing for 5 hr, the mixture was cooled, washed with 10% HCl, and dried ($MgSO_4$). Removal of the solvent gave 2.0 g of **7** as a colorless oil. Compound **7** (2.0 g), conc. HCl (25 ml) and AcOH (25 ml) were refluxed for 15 hr then evaporated to dryness. The resulting mass (1.7 g) was refluxed with conc. H_2SO_4 (2.0 ml), EtOH (60 ml) and benzene (40 ml) for 15 hr. After concentration, the residue was diluted with H_2O, basified with 10% NaOH, and extracted with ether. After drying (K_2CO_3) and removal of the solvent, the residual syrup (1.0 g) was heated at 100° (40 mmHg) for 8 hr. The resulting solid mass was dissolved in benzene, washed with 5% HCl, and dried ($MgSO_4$). Removal of the solvent and recrystallization of the residue from Me_2CO–Et_2O gave 196 mg (11% yield based on **5**) of **8** as colorless/cubes: mp 98—101°. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). MS *m/e*: 257 (M^+). *Anal.* Calcd for $C_{16}H_{19}NO_2$: C, 73.68; H, 7.44; N, 5.44. Found: C, 74.84; H, 7.41; N, 5.47.

8-Hydroxy-6-methyl-1,2,3,4,5,6-hexahydro-1,3-ethano-2,6-methano-3-benzazocine (1)——A mixture of **5** (50 mg, 0.195 mmol) and $LiAlH_4$ (100 mg, 2.7 mmol) in dioxane (3 ml) was refluxed for 6 hr. After cooling, the mixture was treated with H_2O and Rochelle salt solution, extracted with $CHCl_3$, and dried (K_2CO_3). Distillation of the residue from the chloroform solution afforded 42 mg (89%) of a colorless oil: bp 140—150° (1 mmHg) (bath temp.). NMR ($CDCl_3$) δ: 1.32 (3H, s, C_6–Me), 3.69 (3H, s, O–Me), 6.54—6.70 (2H, m, C_7– and C_9–H), 6.94 (1H, d, $J=8$ Hz, C_{10}–H). MS *m/e*: 243 (M^+).

The distillate (42 mg, 0.173 mmol) and HBr (47%, 0.7 ml) were refluxed for 30 min. After evaporation to dryness, the solid mass was recrystallized from MeOH–Me_2CO to give 38 mg (71%) of **1**·HBr: mp 260—263°. *Anal.* Calcd for $C_{15}H_{19}NO \cdot HBr$: C, 58.07; H, 6.50; N, 4.52. Found: C, 58.29; H, 6.48; N, 4.80.

3-Ethoxycarbonylmethyl-6-methyl-8-methoxy-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocine (11)——ClCOOEt (4.0 g) in benzene (30 ml) was added to a refluxing solution of **3** (2.0 g, 8.65 mmol) in benzene (30 ml) during 10 min. The mixture was refluxed for 2 hr, cooled, and washed with 10% HCl. The residual colorless oil (1.9 g) from the dried ($MgSO_4$) solution was refluxed with conc. HCl (20 ml) and AcOH (20 ml) for 22 hr. After concentration *in vacuo*, the pale brown residue was dissolved in H_2O, basified with 10% NaOH, extracted with ether, and dried ($MgSO_4$). Removal of the solvent yielded 1.7 g of a viscous oil, which was distilled to give 1.5 g (80% yield based on **3**) of **9** as a colorless oil: bp 175—185° (1 mmHg). IR ν_{max}^{film} cm^{-1}: 3300 (broad, NH).

A stirred solution of **9** (1.5 g, 6.9 mmol) in 15% H_2SO_4 (50 ml) was treated with CrO_3 (1.25 g, 12.5 mmol) in 15% H_2SO_4 (50 ml) at 0°. The mixture was stirred and heated at 100° for 2 hr. After cooling, the solution was basified with conc. NH_4OH, extracted with ether, and dried ($MgSO_4$). The residue (1.5 g) from the ethereal solution was stirred with $BrCH_2COOEt$ (2.0 g, 12 mmol), K_2CO_3 (10 g) and benzene (100 ml) under reflux for 6 hr. After filtration and removal of the solvent, the residual oil was distilled to yield 1.37 g (63%) of **11** as an orange syrup: bp 180—190° (1 mmHg) (bath temp.). IR ν_{max}^{film} cm^{-1}: 1670 (C=O), 1740 (COOEt). NMR ($CDCl_3$) δ: 1.21 (3H, t, $J=7$ Hz, $COOCH_2C\underline{H}_3$), 1.38 (3H, s, C_6–Me), 2.99 and 2.41 (2H, AB-q, $J=16$ Hz, $NC\underline{H}_2COOEt$), 3.73 (3H, s, O–Me), 4.02 (2H, q, $J=7$ Hz, $COOC\underline{H}_2CH_3$), 6.50—6.68 (2H, m, C_7– and C_9–H), 7.72 (1H, d, $J=8$ Hz, C_{10}–H). MS *m/e*: 317 (M^+).

6-Methyl-8-methoxy-1,2,3,4,5,6-hexahydro-1,3-epoxyethano-2,6-methano-3-benzazocine (2)——A stirred solution of **11** (1.1 g, 3.47 mmol) in MeOH (40 ml) was treated with $NaBH_4$ (2.12 g) at 0° portioniwse during 15 min. After stirring for 2 hr at room temp., the reaction mixture was concentrated, and the residue was dissolved in H_2O, extracted with $CHCl_3$, and dried ($MgSO_4$). The residual oil (0.92 g) from the chloroform solution was refluxed with 10% HCl (100 ml) for 2 hr. The solution was cooled, basified with 10% NaOH, extracted with $CHCl_3$, and dried (K_2CO_3). Removal of the solvent yielded 0.7 g of crude **2**, which was distilled to give 488 mg (55%) of pure **2** as a colorless oil: bp 145—155° (0.5 mmHg) (bath temp.). NMR ($CDCl_3$) δ: 1.32 (3H, s, C_6–Me), 3.72 (3H, s, O–Me), 4.47 (1H, d, $J=5$ Hz, C_1–H), 6.60—6.75 (2H, m, C_7– and C_9–H), 7.24 (1H, d, $J=8$ Hz, C_{10}–H). MS *m/e*: 259 (M^+). Hydrochloride: mp 220—223° (from MeOH–Me_2CO). *Anal.* Calcd for $C_{16}H_{21}NO_2 \cdot HCl$: C, 64.97; H, 7.50; N, 4.74. Found: C, 64.92; H, 7.30; N, 4.50.

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