figures were measured by a Union RA 1300 Stopped Flow Rapid Scan Analyser. After mechanical injection of equal volumes of two kinds of solutions into the reaction cell (optical path length of 1 cm) of the stopped flow apparatus circulated by thermostated H_2O at 25°, the absorption spectra in a range from 415 to 565 nm were recorded on the digital memory at appropreate time intervals and regenerated on an X–Y recorder.

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A New Synthesis of 6,7-Benzomorphan[1]

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A new synthetic route to 6,7-benzomorphan has been developed. 2,2-Dimethyl-7-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (**1**) was cyanomethylated, followed by $LiAlH_4$ reduction and a Wagner-Meerwein rearrangement, to give aminoethyl compound **3**. Treatment of **3** with bromine gave hydrobenz[*e*]indole **4**, which was rearranged to 9-methylene-6,7-benzomorphan **5**. Hydrogenation of the methylene gave 5,9α-dimethyl derivative **6**, from which 5,9α-dimethyl-2′-hydroxy-6,7-benzomorphan (**7**) was obtained.

Keywords——synthesis of benzomorphan; cyanomethylation of tetralone-1; Wagner-Meerwein rearrangement of 1,2,2-trialkyl-1-tetralol; stereospecific reduction of olefin; rearrangement of bromo-hydrobenz[*e*]indole to 6,7-benzomorphan

Many compounds possessing potent analgesic activity have been found from N-substituted 5,9-dimethyl-2′-hydroxy-6,7-benzomorphans, and among these, pentazocine is the one used clinically as a unique non-narcotic analgesic. 5,9-Dimethyl-2′-hydroxy(or methoxy)-6,7-benzomorphan, an important intermediate for the synthesis of the N-substituted derivatives, has been prepared by dealkylation of the N-methyl (von Braun cyanogen bromide procedure)[3] or the N-benzyl derivative (hydrogenolysis).[4] The dealkylation, however, would have been laborious. A more novel method for the synthesis of 6,7-benzomorphan, following the work of Belleau, *et al.*,[5] in which there was projected conversion of hydrobenz[*e*]indole to the 6,7-benzomorphan framework.

The synthesis of 5,9α-dimethyl-2′-hydroxy-6,7-benzomorphan (**7**) from 2,2-dimethyl-7-methoxy-3,4-dihydronaphthalen-1 (2*H*)-one (**1**)[6] is outlined in Chart 1. Cyanomethylation of the α-tetralone **1** with $LiCH_2CN$ gave the cyano alcohol **2**. Compound **2** was reduced with $LiAlH_4$, followed by a Wagner -Meerwein rearrangement with hydrochloric acid, to give 1-(2-aminoethyl)-1,2-dimethyl-1,4-dihydronaphthalene (**3**). It is worthy of note that the exo olefinic compound **3′** was obtained by treatment of **2** with hydrochloric acid for 2—3

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2) Location: *a) Hongo 13, Toyama; b) Hariwara-nakamachi 350–1, Toyama; c) Tawame 1076, Sakado-machi, Saitama.*
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hours at 40°, while compound **3** was obtained by treatment of **3'** (or **2**) for 3—4 days at 40° or 4—5 hours at 50° (the latter procedure gave less yield of **3**). Bromination of the 1,4-dihydronaphthalene **3** with bromine in chloroform gave 4α-bromo-3a,9b-dimethyl-8-methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole hydrobromide (**4**). The stereochemical outcome of this reaction was predicted on the basis of the expected trans addition of bromonium ion and the amino group to the olefinic double bond in **3**. This was supported by the successful rearrangement to the 6,7-benzomorphan compound as the 4β-bromo isomer is probably incapable of this rearrangement. The nuclear magnetic resonance (NMR) spectrum of **4** showed the C-5 proton signal at δ 3.42 as a doublet (J=9.0 Hz) and the C-4 proton signal at δ 4.77 as a triplet (J=9.0 Hz). This coupling feature indicated the C-4 hydrogen to be equatorial-like.

Conversion of **4** into the 9-methylene-6,7-benzomorphan **5** was effected with sodium bicarbonate in dimethyl formamide. Catalytic hydrogenation of the methylene group in **5** over platinum catalyst in methanol afforded 5,9α-dimethyl-2'-methoxy-6,7-benzomorphan **6**, from which the final compound **7** was obtained by refluxing with hydrobromic acid.

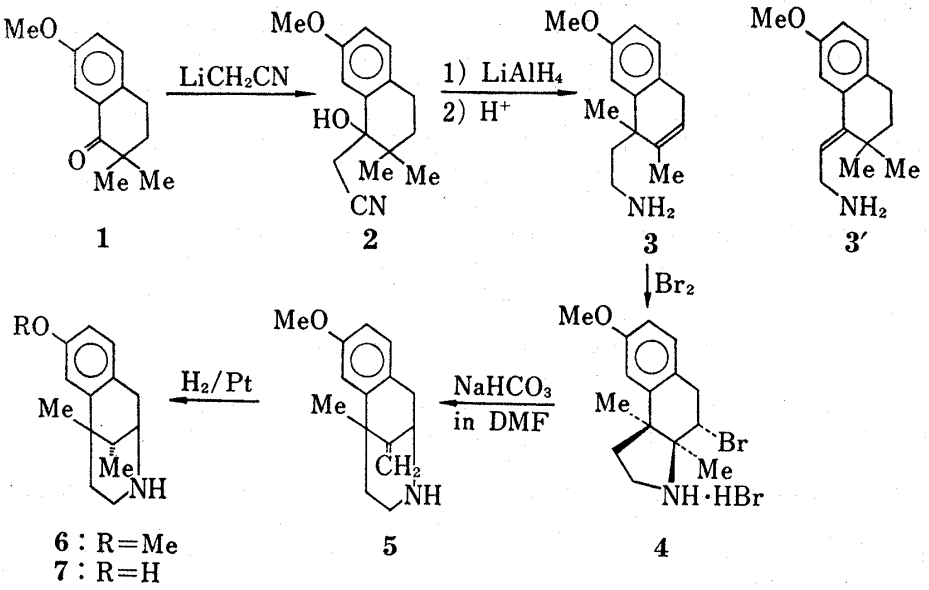

Chart 1

Experimental

All melting points were determined with a micromelting point apparatus (Yanagimoto) and are uncorrected. Microanalyses were performed by Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Toyama. Infrared (IR) spectra were taken on a Hitachi 215 grating infrared spectrometer. NMR spectra were recorded on a JEOL PMX-60 spectrometer with TMS as an internal standard. Mass spectra were recorded on a JEOL JMS-01SG mass spectrometer.

1-Cyanomethyl-2,2-dimethyl-7-methoxy-1,2,3,4-tetrahydro-1-naphthol (**2**)——2,2-Dimethyl-α-tetralone **1**[6] (20 g) in tetrahydrofuran (THF) (120 ml) was added to a suspension of $LiCH_2CN$, prepared from BuLi in hexane (20%, 90 ml) and MeCN (7.3 g) in THF (200 ml) under N_2 and dry ice-acetone cooling, and stirring was continued for 10 min at this temperature. The reaction mixture was poured into H_2O, and the organic layer was separated. The aqueous layer was extracted with ether. The organic layer and the extract were combined, and dried ($MgSO_4$). Evaporation of the solvent gave brown crystals, which were recrystallized from ether to give 21.8 g (90.5%) of **2**, mp 103—104°. IR ν_{max}^{Nujol} cm^{-1}: 3480 (OH), 2250 (CN). NMR ($CDCl_3$) δ: 0.96 (s, 3H) and 1.17 (s, 3H) (C-2 Me_2), 2.00 (s, 1H, OH, exchangeable with D_2O), 3.82 (s, 3H, OMe). Mass spectrum *m/e*: 245 (M^+). *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.35; H, 7.90; N, 5.66.

1-(2-Aminoethyl)-1,2-dimethyl-7-methoxy-1,4-dihydronaphthalene (**3**)——To a suspension of $LiAlH_4$ (6.2 g) in ether (200 ml) was added a solution of **2** (10.5 g) in THF (10 ml) and ether (200 ml) with ice cooling over 2 hr and the resulting mixture was stirred for 3 hr at this temperature. The mixture was treated with

aqueous Rochelle salt solution, and the organic layer was separated. The aqueous layer was extracted with ether. The organic layer and the extract were combined, and extracted with 5% HCl. The aqueous layer was washed with benzene and basified with 10% NaOH, extracted with ether. After drying (K_2CO_3), the solvent was evaporated to give 8.3 g (77.6%) of the amino-alcohol as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 3200, 3400 (OH and NH_2). NMR ($CDCl_3$) δ: 0.83 (s, 3H) and 1.13 (s, 3H) (C-2 Me_2), 3.00 (br. s, 3H, OH and NH_2, exchangeable with D_2O), 3.78 (s, 3H, OMe).

A mixture of the amino-alcohol (11.3 g), ether (200 ml) and conc. HCl (200 ml) was gently refluxed (the bath temperature was kept around 40°) for 2 hr under N_2. A small portion of the aqueous layer was basified with 10% NaOH, extracted with ether. From the dried (K_2CO_3) extract 1-(2-aminoethylidene)-2,2-dimethyl-7-methoxy-1,2,3,4-tetrahydronaphthalene (3′) was obtained as a single product. NMR ($CDCl_3$) δ: 1.10 (s, 6H, C-2 Me_2), 1.50 (s, 2H, NH_2, exchangeable with D_2O), 1.66 (t, J=6.0 Hz, 2H, C-3 H), 2.77 (t, J=6.0 Hz, 2H, C-4 H), 3.62 (d, J=6.5 Hz, 2H, C=C-CH_2-), 3.76 (s, 3H, OMe), 5.53 (t, J=6.5 Hz, 1H, C=C<u>H</u>-CH_2-. Mass Spectrum *m/e*: 231 (M^+). Hydrogen oxalate: mp 184—185.5° (from EtOH). *Anal.* Calcd. for $C_{15}H_{21}ON \cdot C_2H_2O_4$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.70; H, 7.41; N, 4.07.

Reflux of the above reaction mixture was continued for 4 days. After cooling, the aqueous layer was basified with 10% NaOH, extracted with ether. The residual oil of the dried ethereal solution was distilled *in vacuo* to give 8.3 g (79%) of compound **3**, bp 130° (0.3 mmHg). NMR ($CDCl_3$) δ: 1.24 (s, 2H, NH_2, exchangeable with D_2O), 1.38 (s, 3H, C-1 Me), 1.82 (d, J=0.5 Hz, 3H, C-2 Me), 3.30 (m, 2H, C-4 H), 3.80 (s, 3H, OMe), 5.66 (m, 1H, C-3 H). Mass Spectrum *m/e*: 231 (M^+).

4α-Bromo-3a,9b-dimethyl-8-methoxy-2,3,3a,4,5,9b-hexahydro-1*H*-benz[*e*]indole Hydrobromide (4)——To a stirred solution of Br_2 (1.2 g) in $CHCl_3$ (75 ml) was added compound **3** (1.3 g) in $CHCl_3$ (5.6 ml) over 5 min with ice-cooling. After stirring at the same temperature for 1 hr, the solvent was evaporated *in vacuo* to dryness at 30°. The solid residue (1.3 g, 60%) was recrystallized from EtOH to give 0.3 g (13.6%) of pure sample of **4**, mp 209—212° (decomp). IR ν_{max}^{Nujol} cm^{-1}: 2450, 2700 (NH^+_2). NMR (CF_3CO_2H) δ: 1.75 (s, 3H and 1.80 (s, 3H) (C-3a Me and C-9b Me), 3.42 (d, 2H, J=9.0 Hz, C-5 H), 3.98 (s, 3H, OMe), 4.77 (t, J=9.0 Hz, 1H, C-4 H). *Anal.* Calcd. for $C_{15}H_{20}ONBr \cdot HBr$: C, 46.06; H, 5.41; N, 3.58. Found: C, 46.32; H, 5.34; N, 3.40.

2′-Methoxy-5-methyl-9-methylene-6,7-benzomorphan (5)——A mixture of **4** (1.9 g), $NaHCO_3$ (448 mg) and dimethyl formamide (DMF) (80 ml) was stirred and heated at 135° for 1.5 hr. After cooling, the reaction mixture was diluted with H_2O, basified with 10% NaOH, and extracted with ether. Evaporation of the solvent from the dried extract gave crude **5** (1.5 g), which was chromatographed on a silica gel column. Elution with $CHCl_3$–MeOH (9: 1) gave 0.4 g (36%) of pure **5**, bp 145° (bath temperature) (0.45 mmHg). IR ν_{max}^{neat} cm^{-1}: 3300 (NH). NMR ($CDCl_3$) δ: 1.51 (s, 3H, C-5 Me), 1.98 (s, 1H, NH, exchangeable with D_2O), 3.80 (s, 3H, OMe), 4.76—4.86 (m, 2H, C-9 C=CH_2). Mass Spectrum *m/e*: 229 (M^+). Hydrochloride: mp 239—241° (from EtOH). *Anal.* Calcd. for $C_{15}H_{19}ON \cdot HCl$: C, 67.79; H, 7.58; N, 5.27. Found: C, 67.71; H, 7.66; N, 5.49.

2′-Methoxy-5,9α-dimethyl-6,7-benzomorphan (6) and 2′-Hydroxy-5,9α-dimethyl-6,7-benzomorphan (7)——A mixture of **5·HCl** (100 mg) and PtO_2 (0.1 g) in MeOH was shaken in H_2 for 5 hr. After removal of the catalyst and solvent, the residue was dissolved in H_2O and basified with 10% NaOH, extracted with ether, and dried (K_2CO_3). The residual oil of the ethereal solution was distilled *in vacuo* to give 82 mg (94%) of **6**, bp 125° (bath temperature) (0.7 mmHg). IR ν_{max}^{neat} cm^{-1}: 3250 (NH). NMR ($CDCl_3$) δ: 0.82 (d, J= 7.8 Hz, 3H, C-9 Me), 1.36 (s, 3H, C-5 Me), 3.80 (s, 3H, OMe).

Compound **6** (30 mg) and 48% aq. HBr (1 ml) were refluxed for 30 min. After evaporation to dryness, the residue was dissolved in H_2O and basified with conc. NH_4OH to precipitate **7** as crystals, mp 230—233° (lit. mp 232—235°[3]). Yield, 24 mg (86%). Mixed melting point test and comparison of the IR spectrum with an authentic sample[3] confirmed the structure of compound **7**.