2,3,4,5,6,7-Hexahydro-1,6-methano-1*H*-3-benzazonine Derivatives as Analgesics

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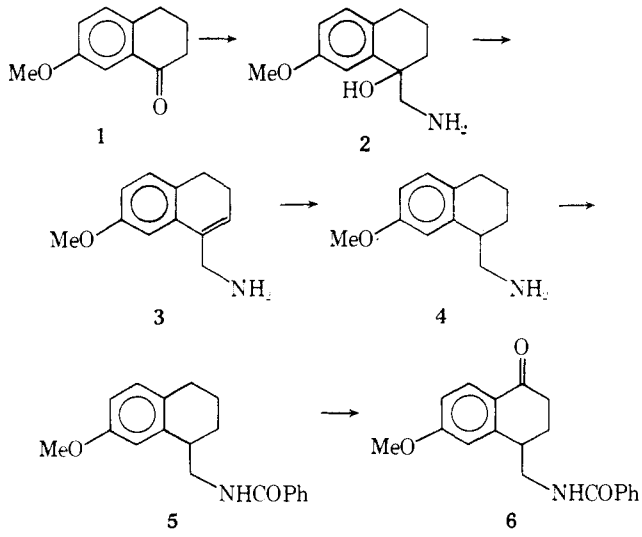
10-Methoxy- (**10**) and 10-hydroxy-3-methyl-2,3,4,5,6,7-hexahydro-1*H*-3-benzazonine (**11**) have been synthesized from 7-methoxy-α-tetralone (**1**) *via* the 1-aminomethyl compound **4**, which was converted to the amino acid derivative **7**. Hydrogenation and cyclization of **7** afforded the lactam **9**, which was reduced with $LiAlH_4$, followed by N-methylation to give **10**, from which **11** was obtained. Compounds **10** and **11** have analgetic activity, and the former was found to be comparable to codeine.

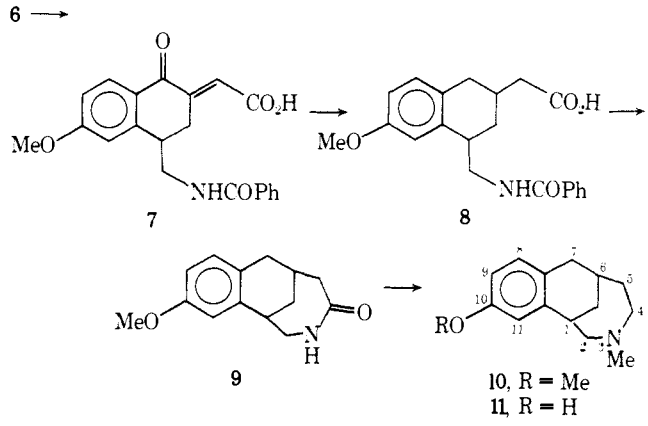
In an attempt to determine some of the structural features that are needed for analgetic activity we have synthesized a series of compounds where ring C of benzomorphan and ring D of morphinan have been modified by enlargement to a seven-membered ring.[1-3] From this group of compounds, some derivatives of 2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine,[4] 2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonine,[5] and 1,3,4,9,10,10a-hexahydro-2*H*-10,4a-methanoiminoethanophenanthrene[3] were found to possess remarkable analgetic activity.

In this paper we wish to describe synthesis and evaluation for analgetic activity of some derivatives of 2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-3-benzazonine, a new member of ring C homobenzomorphans.

Chemistry. Cyanation of 7-methoxy-3,4-dihydronaphthalen-1(2*H*)-one (**1**) with Me_3SiCN[6] and the subsequent reduction with $LiAlH_4$ afforded amino alcohol **2**. Since hydrogenolysis of the hydroxyl group (Pt in acetic acid or Pd/C in methanol–HCl) gave inferior results, compound **2** was converted to 1-aminomethyl-7-methoxy-3,4-dihydronaphthalene (**3**) by refluxing with hydrochloric acid, the structure of which was confirmed from its NMR spectrum. Hydrogenation of **3** afforded a tetralin derivative **4** in good yield.



Compound **4** was derivatized to its *N*-benzoyl derivative **5** followed by oxidation with $Na_2Cr_2O_7$ to give tetralone compound **6**. Condensation of **6** with glyoxylic acid[7] gave an α,β-unsaturated carboxylic acid **7**. On hydrogenating over Pt in MeOH–AcOH–HCl, compound **7** was easily reduced to tetralin compound **8**. Although a stereoisomeric mixture of 1,3-disubstituted tetralins would be anticipated, no attempt was made to separate them because only the cis isomer would cyclize to form lactam **9**.[1] Hydrolysis of the *N*-benzoyl group, esterification of the carboxyl group, and cyclization by heating at 200° afforded the desired lactam **9**.



Lactam **9** was reduced with $LiAlH_4$, followed by N-methylation with HCO_2H–HCHO to give compound **10**, from which the 10-hydroxyl derivative **11** was prepared by refluxing with hydrobromic acid.

Pharmacology. Analgetic activities of compounds **10** and **11** were tested by the method of pressure stimuli on mouse tail[8] after sc administration and groups of ten albino male mice dd strain were tested at five dose levels. ED_{50} values were calculated from the pain reaction by the Litchfield–Wilcoxon method[9] (see Table I). Activity of the methoxyl derivative **10** is comparable to that of codeine or 2′-hydroxy-2-methyl-6,7-benzomorphan[10] and, more noteworthy, surpasses that of the hydroxyl derivative **11**.

Thus, it is of interest to note that the considerable structural change from the 6,7-benzomorphans to the 2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-3-benzazonine molecule still retains analgetic activity.

Experimental Section

Melting points were determined with a Micro melting point apparatus (Yanagimoto) and are uncorrected. Microanalyses were performed by Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Toyama. Where analyses are indicated only by symbols of the elements, the analytical results obtained for these elements were within ±0.4% of the theoretical value. NMR spectra were recorded on a JNM C-60H spectrometer with Me_4Si as an internal standard. Ir spectra were taken on a Japan Spectroscopic IR-E spectrophotometer. Mass spectra were recorded on a JEOL JMS-01SG mass spectrometer.

7-Methoxy-1-aminomethyl-1,2,3,4-tetrahydro-1-naphthol (2). To a stirred solution of **1** (14.7 g) in C_6H_6 (12 ml) was added Me_3SiCN[6] (9.1 g) containing anhydrous ZnI_2 (10 mg) during 20 min under N_2 and with ice cooling. After stirring at 45–55° for 4 hr, the mixture was evaporated in vacuo. The resultant residue (23 g) in ether (100 ml) was added to a suspension of $LiAlH_4$ (5 g) in ether (100 ml) over 40 min under N_2 and at room temperature.

Table I. Analgetic Activities of Homobenzomorphans

Compound	ED_{50}, mmol/kg
10[a]	0.0437 (0.0368–0.0519)[e]
11·HBr[b]	0.176 (0.129–0.247)
Morphine[c]	0.00464 (0.00383–0.00563)
Codeine[d]	0.0232 (0.0204–0.0262)

[a]Administered as lactate in saline. [b]Administered in saline. [c]Administered as hydrochloride in saline. [d]Administered as phosphate in saline. [e]Confidence interval (95%).

After gentle refluxing (1 hr), the mixture was cooled and treated with aqueous Rochelle salt solution. The aqueous layer was extracted with $CHCl_3$. The ethereal layer and the extract were combined and extracted with 5% HCl. The acidic layer was basified with 10% NaOH and extracted with $CHCl_3$. Drying (K_2CO_3) and evaporation of solvent gave 18 g of crude **2**, which was distilled in vacuo to give 16 g of a pure sample of **2** as a colorless oil: bp 160–170° (2 mmHg); ir (neat) 3000–3600 cm^{-1} (NH_2 and OH); NMR ($CDCl_3$) δ 1.50–2.00 (m, 4, C-2 and C-3 H), 2.00 (s, 2, NH_2, exchangeable with D_2O), 2.65 (t, J = 5.0 Hz, 2, C-4 H), 2.80 (s, 2, $-CH_2NH_2$), 3.72 (s, 3, OMe), 6.65 (q, $J_{5,6}$ = 8.0 Hz, $J_{6,8}$ = 3.0 Hz, 1, C-6 H), 6.92 (d, $J_{6,5}$ = 8.0 Hz, 1, C-5 H), 7.00 (d, $J_{8,6}$ = 3.0 Hz, 1, C-8 H). The oxalate had mp 219–220° (from MeOH–Me_2CO). Anal. ($C_{12}H_{17}NO_2 \cdot C_2H_2O_4$) C, H, N.

7-Methoxy-1-aminomethyl-1,2,3,4-tetrahydronaphthalene (4). Compound **2** (3.9 g), 12 *M* HCl (20 ml), and EtOH (100 ml) were refluxed for 1 hr. After evaporation in vacuo to dryness, the residual solid was recrystallized from Me_2CO to give 2.9 g of **3**·HCl as colorless needles of mp 195–197°: NMR (D_2O) δ 2.25 (a pair of t, $J_{3,4}$ = 6.5 Hz, $J_{3,2}$ = 4.5 Hz, 2, C-3 H), 2.60 (t, $J_{4,3}$ = 6.5 Hz, 2, C-4 H), 3.72 (s, 3, –OMe), 3.90 (s, 2, $-CH_2NH_2$), 6.22 (t, $J_{2,3}$ = 4.5 Hz, 1, C-2 H), 6.70 (d, $J_{8,6}$ = 3.0 Hz, C-8 H), 6.78 (q, $J_{6,5}$ = 9.0 Hz, $J_{6,8}$ = 3.0 Hz, 1, C-6 H), 7.10 (d, $J_{5,6}$ = 9.0 Hz, 1, C-5 H).

A mixture of **3**·HCl (2.7 g), PtO_2 (0.3 g), and AcOH (5 ml) in MeOH (45 ml) was shaken in H_2 at room temperature and atmospheric pressure for 10 hr. After removal of catalyst and solvent, the residual oil was dissolved in 5% HCl and washed with ether. The aqueous layer was 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 2.0 g of **4**: bp 120–128° (2 mmHg); ir (neat) 3300, 3400 cm^{-1} (NH_2); NMR ($CDCl_3$) δ 1.40 (s, 2, NH_2, exchangeable with D_2O), 1.60–1.90 (m, 4, C-2 and C-3 H), 2.50–2.90 (m, 5, C-1, C-4 and $-CH_2NH_2$), 3.70 (s, 3, OMe), 6.52 (q, $J_{6,5}$ = 8.0 Hz, $J_{6,8}$ = 2.0 Hz, 1, C-6 H), 6.65 (d, $J_{8,6}$ = 2.0 Hz, 1, C-8 H), 6.90 (d, $J_{5,6}$ = 8.0 Hz, 1, C-5 H). The oxalate had mp 200–202° (from MeOH). Anal. ($C_{12}H_{17}NO \cdot C_2H_2O_4$) C, H, N.

6-Methoxy-4-(benzamidomethyl)-3,4-dihydronaphthalen-1(2*H*)-one (6). To a mixture of **4** (0.5 g), 10% NaOH (10 ml), and ether (20 ml) was added PhCOCl (0.45 g) portionwise at room temperature with vigorous stirring. After stirring (10 min), the ethereal layer was washed with 5% HCl and H_2O and dried ($MgSO_4$). Evaporation of solvent gave 0.85 g of **5**. It was recrystallized from ether–Me_2CO to give a pure sample as colorless needles: mp 119–122°; ir (KBr) 3300 (NH), 1635 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.75–2.00 (m, 4, C-2 and C-3 H), 2.50–3.50 (m, 5, C-1, C-4 and $-CH_2NH-$), 3.80 (s, 3, OMe), 6.40 (br s, 1, NH, exchangeable with D_2O), 6.75 (q, $J_{6,5}$ = 8.0 Hz, $J_{6,8}$ = 2.0 Hz, 1, C-6 H), 6.80 (d, $J_{8,6}$ = 2.0 Hz, 1, C-8 H), 7.07 (d, $J_{5,6}$ = 8.0 Hz, 1, C-5 H), 7.40–7.90 (m, 5, Ph). Anal. ($C_{19}H_{21}NO_2$) C, H, N.

To a stirred mixture of **5** (6.0 g) and $Na_2Cr_2O_7$ (9.1 g) in 1 *N* H_2SO_4 (300 ml) and AcOH (480 ml) was added 10 *N* H_2SO_4 (600 ml) at room temperature during 2 hr. After stirring (15 hr), the mixture was diluted with H_2O (2 l.) and extracted with $CHCl_3$. The extract was washed with 5% $NaHCO_3$, dried ($MgSO_4$), and evaporated to give 6 g of crude **6**, which was recrystallized from Me_2CO to give 5.1 g of pure sample as colorless cubes: mp 153–155°; ir (KBr) 3300 (NH), 1680 (Ar-C=O), 1640 cm^{-1} (NHC=O); NMR ($CDCl_3$) δ 2.00–3.50 (m, 7, C-2, C-3, C-4 H and $-CH_2NH-$), 3.85 (s, 3, OMe), 6.60 (br s, 1, NH, exchangeable with D_2O), 6.78 (d, $J_{5,7}$ = 2.0 Hz, 1, C-5 H), 6.90 (q, $J_{7,8}$ = 8.0 Hz, $J_{7,5}$ = 2.0 Hz, 1, C-7 H), 7.30–7.90 (m, 5, Ph), 8.00 (d, $J_{8,7}$ = 8.0 Hz, 1, C-8 H). Anal. ($C_{19}H_{19}NO_3$) C, H, N.

6-Methoxy-4-(benzamidomethyl)-2-carboxymethylene-3,4-dihydronaphthalen-1(2*H*)-one (7). To an ice-cooled mixture of $HIO_4 \cdot 2H_2O$ (4.44 g), NaOH (0.77 g), and H_2SO_4 (0.36 ml) in H_2O (30 ml) was added a solution of tartaric acid (2.94 g) in H_2O (6 ml). After stirring at room temperature (30 min), to this mixture were added **6** (5.1 g) in EtOH (10 ml) and NaOH (3.11 g) in H_2O (62 ml) and EtOH (50 ml). The mixture was then stirred at room temperature for 15 hr and at 60° for 10 min, cooled, diluted with H_2O, and washed with ether. Acidification of the alkaline layer yielded 4.5 g of colorless plates, which was recrystallized from EtOH to give pure **7**: mp 230–234°; ir (KBr) 3300 (NH), 3300–2400 (COOH), 1710 (COOH), 1670 (Ar-C=O), 1630 cm^{-1} (NHC=O). Anal. ($C_{21}H_{19}NO_5$) C, H, N.

10-Methoxy-2,3,6,7-tetrahydro-1,6-methano-1*H*-3-benzazonin-4(5*H*)-one (9). Hydrogenation of **7** (5.0 g) over PtO_2 (1.5 g) in 10% HCl (20 ml), MeOH (80 ml), and AcOH (80 ml) for 10 hr gave a residual oil (8, 5 g). Compound **8** (5 g) was refluxed with 6 *N* HCl (100 ml) for 9 hr, cooled, washed with ether, and evaporated to give 3.0 g of yellow viscous syrup. The yellow syrup (3.0 g), EtOH (60 ml), C_6H_6 (40 ml), and H_2SO_4 (2 ml) were refluxed for 10 hr. After evaporation, the residue was dissolved in H_2O, basified with 10% NaOH, extracted with ether, and dried (K_2CO_3). Evaporation of the solvent afforded a viscous oil [1.5 g; ir (neat) 3300, 3400 (NH_2), 1750 cm^{-1} (CO_2Et)] which was heated at 200° (40 mmHg) for 1 hr and then distilled in vacuo to give 0.4 g of lactam **9**, bp 200–230° (bath temperature, 0.15 mmHg). The distillate which solidified on standing was recrystallized from Me_2CO to give 366 mg of colorless prisms of **9**: mp 148–151°; ir (KBr) 3250 (NH), 1660 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.70–3.55 (m, 10, aliphatic H), 3.76 (s, 3, OMe), 5.30 (br s, 1, NH, exchangeable with D_2O), 6.52 (d, $J_{11,9}$ = 2.0 Hz, 1, C-11 H), 6.69 (q, $J_{9,8}$ = 8.5 Hz, $J_{9,11}$ = 2.0 Hz, 1, C-9 H), 7.01 (d, $J_{8,9}$ = 8.5 Hz, 1, C-8 H); mass spectrum *m/e* 231 (M^+). Anal. ($C_{14}H_{17}NO_2$) C, H, N.

10-Methoxy- (10) and 10-Hydroxy-3-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-3-benzazonine (11). A mixture of **9** (266 mg) and $LiAlH_4$ (100 mg) in dioxane (30 ml) was refluxed for 8 hr. After cooling, the mixture was treated with H_2O and Rochelle salt, extracted with $CHCl_3$, and dried (K_2CO_3). Distillation of the residue of the chloroform solution gave 202 mg of colorless oil, bp 140–150° (bath temperature, 1 mmHg). The distillate (202 mg), HCO_2H, and HCHO (37%, 1.3 ml) were heated on a water bath for 1.5 hr. After evaporation to dryness, the residual oil was dissolved in 5% HCl, washed with C_6H_6, basified with 10% NaOH, extracted with $CHCl_3$, and dried (K_2CO_3). After evaporation of the solvent, the residual oil was distilled in vacuo to give 182 mg of **10**: bp 135–145° (bath temperature, 1 mmHg); ir (neat) 2780 cm^{-1} (NMe); NMR ($CDCl_3$) δ 1.40–3.20 (m, 12, aliphatic H), 2.25 (s, 3, NMe), 3.70 (s, 3, OMe), 6.60 (q, $J_{9,8}$ = 8.0 Hz, $J_{9,11}$ = 2.0 Hz, 1, C-9 H), 6.72 (D, $J_{11,9}$ = 2.0 Hz, 1, C-11 H), 6.90 (d, $J_{8,9}$ = 8.0 Hz, 1, C-8 H); mass spectrum *m/e* 231 (M^+).

Compound **10** (110 mg) and 48% HBr (1.5 ml) were refluxed for 30 min. Evaporation and recrystallization from MeOH–Me_2CO gave 111 mg of **11**·HBr as colorless crystals of mp 232–236°: ir (KBr) 3280 (OH), 2700 cm^{-1} ($\equiv N^+H$); NMR (CD_3OD) δ 1.20–3.85 (m, 12, aliphatic H), 2.81 (s, 3, $\equiv N^+Me$), 6.61 (q, $J_{9,8}$ = 8.0 Hz, $J_{9,11}$ = 3.0 Hz, 1, C-9 H), 6.72 (d, $J_{11,9}$ = 3.0 Hz, 1, C-11 H), 6.94 (d, $J_{8,9}$ = 8.0 Hz, 1, C-8 H). Anal. ($C_{14}H_{19}NO \cdot HBr$) C, H, N.

References and Notes

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