1-Phthalimido-8-(tosyloxy)-3,6-dioxaoctane (9). To a solution of **8** (5.0 g, 0.018 mol) in dry pyridine (20 mL) was added over a 1-h period *p*-toluenesulfonyl chloride (6.82 g, 0.036 mol) at 0–5 °C. After stirring for 3 h at 23 °C, the mixture was poured onto a mixture of HCl (25 mL) and ice, and the product was extracted with EtOAc (25 mL × 4). After removal of the solvent in vacuo, the crude product was chromatographed on silica gel with EtOAc–hexane (1:1) to give an oil (6 g, 77%), which solidified upon cooling: mp 80–81 °C; R_f 0.33 (silica gel, EtOAc–hexane, 1:1); EIMS, *m/e* 432 (M − 1); NMR ($CDCl_3$) δ 7.84 and 7.71 (4 H, d and m, phthalimide, Ar), 7.77 and 7.44 (4 H, q, Ts, Ar), 4.18–3.48 (12 H, t and m, CH_2O), 2.44 (3 H, s, CH_3). Anal. ($C_{21}H_{23}NO_7S$), C, H, N.

1-Phthalimido-8-(β-naltrexamino)-3,6-dioxaoctane Dihydrochloride (6·2HCl). A mixture of **9** (650 mg, 1.5 mmol), β-naltrexamine **5** (342 mg, 1 mmol), and $NaHCO_3$ (840 mg) in toluene–diglyme (15 mL, 2:1) was heated under N_2 at 110 °C for 10 h. After filtration and removal of solvents in vacuo, the crude product was dissolved in 0.5 N HCl (10 mL) and extracted with EtOAc (25 mL × 3). The aqueous phase was rendered basic (pH 9) with NH_4OH, and the liberated free base was extracted with EtOAc (25 mL × 4). After removal of the solvent in vacuo, the crude product was chromatographed on silica gel with EtOAc–MeOH–NH_4OH (85:15:0.5) to give 300 mg (50%) of **6**, R_f 0.31 (EMA, 85:15:1), which was converted to the HCl salt (hygroscopic); mp 105–110 °C; CIMS, *m/e* 603 (M^+); NMR (Me_2SO-d_6) δ 6.85 and 6.76 (2 H, q, Ar), 7.85 (4 H, m, phthalimide, Ar), 4.92 (1 H, d, C-5 H), 3.81–3.50 (12 H, m, CH_2O); IR (KBr) cm^{-1} 1777 and 1715 (C=O, phthalimide). Anal. ($C_{34}H_{41}N_3O_7$·2HCl·0.5H_2O) C, H, N.

1-Amino-8-(β-naltrexamino)-3,6-dioxaoctane Trihydrochloride (2·3HCl). A solution of 6·2HCl (340 mg, 0.563 mmol) and hydrazine (96 mg, 3 mmol) in EtOH (5 mL) was stirred at 23 °C for 2 days. The solvent was removed in vacuo and the residue was stirred at 23 °C with HCl (1 N, 10 mL) for 5 h. After removal of the insoluble phthalhydrazide by filtration and evaporation of the solvent in vacuo, the crude product was chromatographed on silica gel with EtOAc–MeOH–NH_4OH (80:20:1) to give **2** an oil (229 mg, 0.48 mmol, 96%); R_f 0.35 (EMA, 50:50:5). The free base was converted to the 3HCl salt with 1 N HCl in 2-propanol; mp 190–193 °C dec; EIMS, *m/e* 472.9 (M^+); NMR (Me_2SO-d_6) δ 9.58 (1 H, s, OH phenolic), 9.37 (1 H, br s, H^+N), 8.96 (2 H, br, nal-N^+H_2), 8.12 (3 H, br s, N^+H_3), 6.80 and 6.67 (2 H, q, *J* = 8.2 Hz, Ar), 6.43 (1 H, br s, C-14 OH), 5.00 (1 H, d, *J* = 7.1 Hz, C-5 H), 3.78–3.58 (12 H, t and m, CH_2O). Anal. ($C_{26}H_{39}N_3O_5$·3HCl·3H_2O) C, N; H: calcd, 7.1; found, 8.09.

1-Guanidino-8-(β-naltrexamino)-3,6-dioxaoctane Sulfate (3·1.5H_2SO_4). A solution of **2** (46 mg, 0.097 mmol) and methyl isothiourea sulfate (28 mg, 0.1 mmol) in aqueous ethanol (50%, 3 mL) was stirred at 100 °C for 25 h. Sulfuric acid (1.8 N, 2 mL) then was added to the cold mixture. After removal of solvents in vacuo, the product was purified by gel filtration on Sephadex (LH-20) with MeOH to give the product, mp 155–160 °C (foaming); R_f 0.19 (EMA, 50:50:10); NMR (Me_2SO-d_6) δ 9.45 (1 H, s, OH phenolic), 7.30 (5 H, br s, $NHC(NH_2)_2^+NH_2$), 6.68 and 6.61 (2 H, q, *J* = 8 Hz, Ar), 4.96 (1 H, d, C-5 H), 3.88–3.45 (12 H, m, CH_2O); ^{13}C NMR 157.1 ($NHC(NH_2)_2^+$), 69.80, 69.64, and 69.23 ppm (CH_2O). Anal. ($C_{27}H_{41}N_5O_5$·1.5H_2SO_4·1.5H_2O) C, H.

1-(Benzylamino)-8-(β-naltrexamino)-3,6-dioxaoctane Trihydrochloride (4·3HCl). To a refluxing toluene (15 mL) solution of triethylene glycol ditosylate[12] (4.0 g, 8.76 mmol) containing $NaHCO_3$ (1 g) was added over a 2-h period 1 g of β-naltrexamine **5** in 15 mL of toluene–diglyme (2:1). The reaction was conducted under N_2 at 110 °C for an additional 5 h. After filtration and removal of solvents in vacuo, the excess of ditosylate was removed by dissolving the crude product in 1 N HCl (10 mL) and extracted with EtOAc (30 mL × 3). The aqueous phase containing the product was basified with NH_4OH (pH 9) and extracted with EtOAc (25 mL × 5). After removal of the solvent in vacuo, the crude intermediate compound **7**[1] was purified by gradient elution chromatography using silica gel and EtOAc–MeOH–NH_4OH (99:1:0.5 to 80:20:1). The product (440 mg, 0.7 mmol) was isolated as a glass: R_f 0.67 (EMA, 70:30:4); CIMS, *m/e* 455 (M − TsOH); NMR ($CDCl_3$) δ 7.83 and 7.40 (4 H, q, Ts, Ar), 6.71 and 6.54 (2 H, q, *J* = 8.2 Hz, Ar), 4.51 (1 H d, *J* = 7.97 Hz, C-5 H), 3.98–3.57 (12 H, m, CH_2O). To a solution of **7** (160 mg, 0.28 mmol) in toluene–diglyme (5 mL, 2:1) containing $NaHCO_3$ (120 mg) was added a solution of benzylamine (61 mg, 0.57 mmol) in toluene (1 mL). The reaction that was conducted under N_2 was stirred at 110 °C for 6 h. After filtration and removal of solvent in vacuo, the crude product was chromatographed on silica gel with EtOAc–MeOH–NH_4OH (85:15:1) to give the **4** as an oil (30 mg, 0.053 mmol), which was converted to the 3HCl salt (hygroscopic); R_f 0.25 (EMA, 80:20:2); CIMS, *m/e* 563 (M^+); NMR (D_2C exchanged in Me_2SO-d_6) δ 7.47 (5 H, m, Ar), 6.82 (2 H, Ar), 4.98 (1 H, d, C-5 H), 3.92–3.52 (12 H, m, CH_2O). Anal. ($C_{33}H_{45}N_3O_5$·3HCl·3H_2O) C, H; N: calcd, 5.80; found, 5.16.

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Additions and Corrections

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Reinhard Sarges,* Harry R. Howard, Kathy M. Donahue, Williard M. Welch, Beryl W. Dominy, Albert Weissman, B. Kenneth Koe, and Jon Bordner: Neuroleptic Activity of Chiral *trans*-Hexahydro-γ-carbolines.

Page 19. The supplementary material paragraph was inadvertently omitted. It should read as follows: Listings of coordinates and bond angles and distances, anisotropic temperature factors, hydrogen coordinates, and observed and calculated structure factors and a stereoscopic view of molecule **8** are available as supplementary material (26 pages). Ordering information is given on any current masthead page.