(0.07 mL, 0.53 mmol) in the presence of NMM (0.06 mL, 0.55 mmol). A solution of the amino component **7** (0.25 g, 0.46 mmol) in DMF (2 mL) was added, followed by NMM (0.05 mL, 0.46 mmol). Workup according to general procedure (b) afforded a crude product, which was purified by chromatography on a column (2.5 × 50 cm) loaded with silica gel (Merck, 70–230 mesh) and eluted with $CHCl_3$/MeOH (95:5). The product obtained from chromatography was recrystallized from EtOAc–petroleum ether. Yield: 0.17 g (48%); mp 125–126 °C; $[\alpha]^{25}_D$ –61.8° (*c* 0.5, AcOH); TLC R_f (A) 0.59. Anal. ($C_{39}H_{56}N_6O_7S$) C, H, N.

HCl·Phe-Phe-Pro-Leu-Met-NH_2 (9). Compound **8** was deprotected according to the general procedure and the resulting product **9** (0.11 g, yield: 95%) was used without further characterization.

pGlu-Phe-Phe-Pro-Leu-Met-NH_2 (10). pGlu-OH (0.027 g, 0.21 mmol), dissolved in DMF (0.5 mL), was reacted with IBCF (0.023 mL, 0.17 mmol) in the presence of NMM (0.024 mL, 0.21 mmol). A solution of the amino component **9** (0.090 g, 0.13 mmol) in DMF (0.5 mL) was added, followed by NMM (0.015 mL, 0.13 mmol). Workup according to general procedure (a) yielded 0.02 g (20%) of (10); mp 118–121 °C. The product was pure in HPLC (H_2O/MeOH, 30:70, elution rate 1.5 mL/min, detection at 210 nm). TLC R_f (A) 0.32, R_f (B) 0.63; MS, *m/e* 764 $(M)^+$; FAB-MS, *m/e* 764 $(M)^+$, 765 $(M + H)^+$. Amino acid analysis: Glx 0.95, Phe 1.90, Pro 0.85, Leu 1.00, Met 0.95 (calcd: Glx 1.0, Phe, 2.0, Pro 1.0, Leu 1.0, Met 1.0).

Biological Assays. Materials. Substance P and substance P methyl ester were purchased from Sigma, St. Louis, MO. Neurokinin A and neurokinin B were obtained from Cambridge Research Biochemicals, Harston, U.K. Neurokinin A was also purchased from Peninsula San Diego, CA. $[pGlu^6]SP_{6-11}$ was synthesized as described elsewhere.[17,25]

Isolated Smooth Muscle Preparations. Isolated smooth muscle preparations were suspended in a 10-mL organ bath containing Tyrode's solution (composition in mM: NaCl 118, KCl 4.7, $CaCl_2$ 1.8, $MgCl_2$ 0.5, NaH_2PO_4 1.0, $NaHCO_3$ 25, and glucose 10), gassed with a 95% O_2–5% CO_2 mixture and maintained at 34 °C. Contractions were recorded isotonically. Peptides were applied at 2–3-min intervals with less than 30-s contact time (guinea pig ileum/rat duodenum) or at 15–30-min intervals with a contact time of 1–3 min (hamster urinary bladder). Potentiation of electrically stimulated rat vas deferens contraction was determined as described by Lee et al.[7] At the beginning of a desensitization experiment, the guinea pig ileum was first incubated with a high dose (10^{-7} M) of agonist until the response had faded to the base-line level (2–4 min). The tissue was then washed and immediately reincubated with the agonist (10^{-7} M) for 2 min. The contraction caused by a test peptide was then recorded. All test peptides produced similar maximal contractions in a given test preparation. Relative potencies were calculated from EC_{50} values (concentration of agonist producing 50% of the maximal contraction).

K^+ Release from Rat Parotid Slices. This assay was performed as described before.[15]

Registry No. 1, 2280-69-5; **2**, 2280-68-4; **3**, 2131-00-2; **4**, 101760-39-8; **5**, 101760-44-5; **6**, 101760-40-1; **7**, 101760-41-2; **8**, 101760-42-3; **9**, 101760-43-4; **10**, 79775-19-2; Boc-Leu-OH, 13139-15-6; HCl·Met-OMe, 2491-18-1; Boc-Pro-OH, 15761-39-4; Boc-Phe-OH, 13734-34-4; pGlu-OH, 98-79-3.

(*S*)-3-[(Benzyloxy)methyl]morpholine Hydrochloride: A Nonstimulant Appetite Suppressant without Conventional Neurotransmitter Releasing Properties

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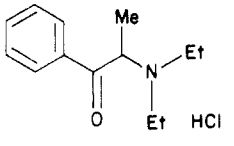
The synthesis and appetite-suppressant activity of (*S*)-3-[(benzyloxy)methyl]morpholine hydrochloride (**3**) in dogs are reported. The oral ED_{50} for appetite suppression in dogs of **3** was 12 mg/kg, and it was tolerated up to 200 mg/kg. **3** had no inhibitory effect on the release or uptake of noradrenaline, dopamine, or serotonin at 10^{-5} M. The (*R*) enantiomer (**4**) of **3** was not anorexiant.

Obesity, which affects some 30% of the adult population of the developed nations of the world, is a major risk factor for cardiovascular disease and non-insulin-dependant diabetes mellitus,[1] as well as creating social problems for the patient. Therapies for obesity range from slimming clubs, low-calorie diets, and behavioral modification to appetite suppressants and surgery but are in general ineffective. Obesity develops when food intake exceeds energy expenditure. For this reason the first choice for treatment is to prescribe a calorie-restricted diet. Generally two phases of weight loss occur: a short period of rapid loss related to fluid depletion followed by a much slower but significant rate of weight reduction. During this second period of treatment the patient may benefit from an appetite suppressant agent to assist with diet compliance. Currently used appetite suppressants such as amphetamines have serious side effects, including stimulant and cardiovascular actions.[2] This type of appetite suppressant, of which diethylpropion (1) is an example, is thought to exert its effect on food intake by acting through adrenergic and dopaminergic mechanisms at the feeding center in the hypothalamus.[3] Fenfluramine (**2**) does not depend on catecholamines for its appetite suppressant effect but is serotoninergic, giving the different side-effect profile of sedation and gastrointestinal actions. This involvement of neurotransmitters in the mechanisms of appetite sup-



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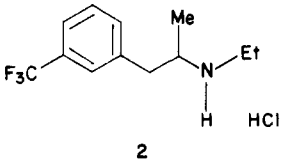

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† Chemistry Department.
‡ Bioscience Department.

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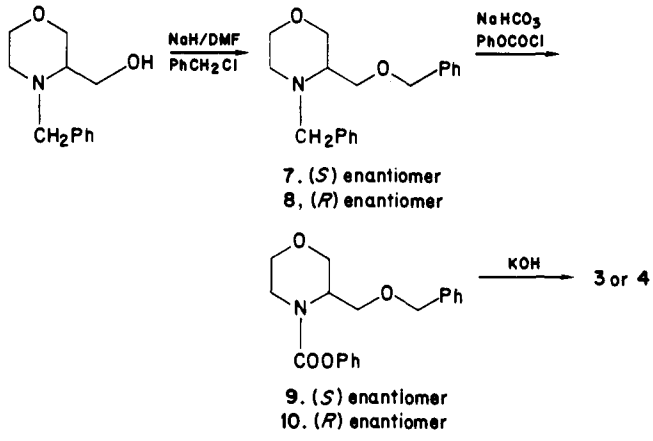
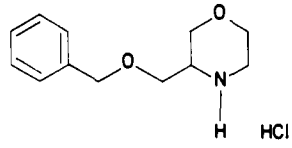
Scheme I



7. (*S*) enantiomer
8. (*R*) enantiomer
9. (*S*) enantiomer
10. (*R*) enantiomer

pression is possibly also responsible for the undesirable side effects associated with the use of appetite-suppressant drugs in man. We describe a novel compound, (*S*)-3-[(benzyloxy)methyl]morpholine hydrochloride (**3**), which is not closely related in structure to amphetamine.



3. (*S*) enantiomer
4. (*R*) enantiomer

Chemistry. Morpholine **3** and the corresponding (*R*) enantiomer **4** were prepared from the appropriate chiral morpholine methanols[4] by alkylation with benzyl chloride as shown in Scheme I. The resulting enantiomers **3** and **4** showed equal and opposite optical rotations in polarized light, and the optical purity of **3** was validated by HPLC examination of a derivative made with the chiral reagent (+)-MPTA.[5]

Pharmacology. The appetite-suppressant activity of **3** was initially determined in mature beagle dogs trained to a 4-h feeding period daily, during which they had free access to meat. In the evaluation of **3**, groups of three dogs were dosed orally 1 h before their feeding period with 10 mg/kg of test compound in soft gelatin capsules. Food consumption was determined by weighing the food remaining at 1 and 2 h after the beginning of the feeding period. In the standard test all dogs received a placebo for 2 days, and then one group received drug while a parallel group received a placebo for a further 3 days. A comparison of the average food consumed on placebo days 1 and 2 of the test, against that on drug-dosed days 3, 4, and 5 demonstrated for **3** a 51% reduction in food consumed at 1 h and 47% at 2 h. The placebo group in the same test showed an increase in food consumption of 18% at 1 h and 14% at 2 h. These results compare with a reduction of 90% at 1 h and 85% at 2 h for diethylpropion (**1**) dosed at 5 mg/kg po, which is a clinically used amphetamine analogue with attenuated stimulant properties. To obtain a more precise definition of potency, five pairs of dogs were allocated at random to one of four oral-dosed treatment regimes at 5, 10, 15, and 20 mg/kg and an undosed placebo pair of dogs, on successive days in a Latin Square Design. In this acute test **3** had an ED_{50} for the 1-h effect of 12 mg/kg compared with 2 mg/kg for **1**. When the feeding period was extended to 4 h, both compounds had a similarly diminished effect, indicating a biological half-life of 2–3 h. One of the failings of existing appetite suppressants is the loss of efficacy on chronic drug dosing. Therefore, three dogs were given a daily oral dose of 15 mg/kg of **3** for 3 weeks, when the mean reduction in food intake at 2 h after dosing for the first 3 days of the test was 53% but had not changed, within experimental error, at 56% during the last 3 days. This contrasts with a reduction of 86% to an increase of 5% for **1** after oral dosing at 3 mg/kg under a similar test regime. At the end of this chronic dosing period, food intake returned quickly to the control range. Dogs given oral doses of >200 mg/kg of **3** were reported to be nervous and hyperactive to stimuli, but there was no evidence of stimulant activity or stereotypy. Under similar test conditions, **1** caused overt stimulation at 5 mg/kg and stereotypy at higher doses. Fenfluramine (**2**) showed moderate sedation at 5 mg/kg.

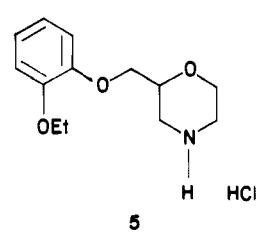
In vitro experiments showed[6] that morpholine **3** did not block the reuptake of noradrenaline, dopamine, or serotonin into rat brain synaptosomes (IC_{50} >10^{-5} M). Similarly, it had no effect at concentrations of up to 10^{-5} M on release of these neurotransmitters, by either pot incubations or superfusion of rat brain slices preloaded with labeled transmitter.

Whereas the threshold concentration of **3** for release of dopamine and serotonin from rat brain synaptosomes was >10^{-5} M, it was 10^{-7} and 10^{-6} M, respectively, for amphetamine. Serotonin release occurred at concentrations of 10^{-7} M of **2**.

In a multiobservational screen in mice designed to reveal CNS actions such as sedation and motor and convulsive effects, no activity was seen for **3** at a sc dose of 300 mg/kg. Experiments in conscious dogs at iv doses of 5 mg/kg showed no effect of **3** on heart rate or blood pressure. In a dosing study in mice, no significant toxic effects were seen after four daily doses of **3** at 1 g/kg.

Discussion

The appetite-suppressant activity seen with **3** was significantly less than that seen with clinically available anorexiant agents. The lower level of activity was however sufficient to predict clinical use and was offset by the absence of CNS and cardiovascular effects in conscious dogs. These results suggest that **3** would be free from the side effects that restrict the use of currently available anorexiants. This view is supported by the absence of effects on neurotransmitter levels in vitro. Despite the difference in the pharmacological profile of **3** and that of commercially used anorexiants, there are some centrally acting compounds with structural similarity to **3**. Thus, **5** and **6**, which are closely related to **3**, have been reported to be appetite suppressants.[7,8] Viloxazine (**5**), however,



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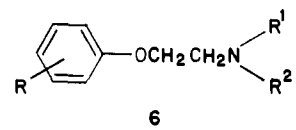

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is an antidepressant drug and is reported to block the reuptake of noradrenaline. Its (S) enantiomer shows[7] greater anorexiant potency than the (R) enantiomer, which parallels the relationship between appetite suppression and chirality found for **3**. The side-chain oxygen of **5** is separated from the morpholine-ring nitrogen atom by three saturated carbon bonds. In contrast the corresponding separation in **3** is two carbon bonds. This differing relationship of heteroatoms may be involved in the expression of different biological profiles by **3** and **5**. The phenoxyalkylamines of general formula **6** show a different side-effect profile to **3**. They were not further developed,[8] due to stimulant and convulsant properties found on dosing to cats.

The (R)-enantiomer **4** corresponding to **3** gave an increase of 13% in food intake at 1 h after oral dosing to dogs at 10 mg/kg, which showed that a chiral molecule was required for anorexiant activity. This suggested the involvement of a receptor in the pharmacological response.

In conclusion, **3** is a novel anorexiant that has a pharmacological profile distinct from commercially available appetite-suppressant drugs.

Experimental Section

Melting points are uncorrected. NMR were determined on a Varian EM390 (90 MHz) spectrometer. Spectral data were consistent with the assigned structures. Where analyses are indicated only by symbols, elementary analyses are within ±0.4% of the theoretical values.

(S)-4-Benzyl-3-[(benzyloxy)methyl]morpholine (7). (S)-4-Benzyl-3-(hydroxymethyl)morpholine (17.0 g, 80.2 mmol) was added during 40 min to stirred NaH (50% w/w dispersion in oil; 4.2 g, 87.5 mmol) in anhydrous DMF (80 mL) under N_2. the mixture was heated to 40 °C and cooled to room temperature. Benzyl chloride (10 mL, 86.7 mmol) in anhydrous DMF (20 mL) was added and the mixture heated at 80–85 °C for 7 h. The DMF was evaporated and the residue shaken with EtOAc and H_2O. The EtOAc phase was extracted with excess of 2 N HCl and the acid phase made alkaline with 30% w/w NaOH solution. The liberated oil was extracted with EtOAc and the extract washed with brine, dried ($MgSO_4$), and evaporated to give as an oil **7**: 19.7 g (80%); $[\alpha]^{22}_D$ +49.7° (c 1, CH_2Cl_2). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

(R)-4-Benzyl-3-[(benzyloxy)methyl]morpholine (8). **8** was prepared from the corresponding (R) morpholine in a manner similar to that for **7**. It was obtained as a colorless oil: 50%; $[\alpha]^{22}_D$ −50.7° (c 1, CH_2Cl_2). Anal. ($C_{19}H_{23}NO_2$) C, H, N.

(S)-3-[(Benzyloxy)methyl]-4-(phenoxycarbonyl)morpholine (9). Phenyl chloroformate (25 mL, 198 mmol) and $NaHCO_3$ (17.6 g, 209 mmol) were added to stirred **7** (17.7 g, 60 mmol) in CH_2Cl_2 (400 mL). The mixture was stirred 16 h at room temperature and evaporated. The residue was chromatographed on silica gel ($PhCH_3$). Elution with 25% v/v EtOAc in $PhCH_3$ gave **9** as a colorless oil: 15.0 g (77%); $[\alpha]^{22}_D$ +46° (c 1, CH_2Cl_2). Anal. ($C_{19}H_{21}NO_4$)C, H, N.

(R)-3-[(Benzyloxy)methyl]-4-(phenoxycarbonyl)morpholine (10). **10** was prepared from the corresponding (R)-benzylmorpholine (**8**) in a manner similar to that of **9**. It was obtained as a colorless oil: 76%; $[\alpha]^{22}_D$ −44.9° (c 1, CH_2Cl_2). Anal. ($C_{19}H_{21}NO_4$) C, H, N.

(S)-3-[(Benzyloxy)methyl]morpholine Hydrochloride (3). A solution of **9** (15.0 g, 46 mmol) and KOH (15.0 g, 267 mmol) in H_2O (75 mL) was heated under reflux for 16 h. The solvent was evaporated and the residue shaken with EtOAc and H_2O. The EtOAc phase was washed with brine and extracted with 2 N HCl. The acid was made alkaline with 30% w/w NaOH and extracted with EtOAc. The EtOAc was washed with brine, dried ($Mg SO_4$), and evaporated. The residue was treated with *i*-PrOH that had been saturated with HCl. The colorless solid was collected and recrystallized from *i*-PrOH to give **3** as a colorless solid: 6.2 g (56%); mp 188–190 °C; free base $[\alpha]^{22}_D$ −6° (c 1, CH_2Cl_2). Anal. ($C_{12}H_{18}ClNO_2$) C, H, N.

(R)-3-[(Benzyloxy)methyl]morpholine Hydrochloride (4). **4** was prepared from the corresponding morpholine **10** in a manner similar to that of **3**. It was obtained as a colorless solid: mp 187–189 °C; 54%; free base $[\alpha]^{22}_D$ + 5.6° (c 1, CH_2Cl_2). Anal. ($C_{12}H_{18}ClNO_2$) C, H, N.

Dog Anorexiant Test. Exbreeder female dogs were trained to a daily 4-h feeding period with unlimited access to meat. Food consumed by each dog in the week preceding the test was recorded, and the dogs were randomized into a test group of three dogs and a control group of three dogs. Test compound was dosed in Parke Davis gelatin capsules at 10 mg/kg, and control dogs were dosed empty capsules. All dogs were dosed placebo for 2 days, 1 h before the start of the feeding period and with test compound/placebo on days 3, 4, and 5. Food remaining was weighed 1 and 2 h after the start of the feeding period. The mean food intake for days 1 and 2 was found for each dog to give control values for the time intervals 0–1 and 0–2 h of the feeding period. The percentage change of the food intake for days 3, 4, and 5 was calculated for each dog. The mean percentage change was found for each group of three dogs. The mean of the percent change for days 3, 4, and 5 was taken as the final result. Each test had a control group in order to be certain that test results could not be explained in terms of control variability.

Registry No. **3**, 101376-19-6; **3** (free base), 101376-27-6; **4**, 101376-20-9; **4** (free base), 101376-28-7; **7**, 101376-21-0; **8**, 101376-22-1; **9**, 101376-23-2; **10**, 101376-24-3; $PhCH_2Cl$, 100-44-7; $ClCO_2Ph$, 1885-14-9; (S)-4-benzyl-3-(hydroxymethyl)morpholine, 101376-25-4; (R)-4-benzyl-3-(hydroxymethyl)morpholine, 101376-26-5.