gel G; $Et_2NH$–EtOAc, 1:20). Anal. ($C_{14}H_{22}NO_2Cl$) C, H, N, Cl.

***cis*-N-Acetyl-2-(3,4-dimethoxybenzyl)cyclopentylamine (5).** Acetyl chloride (1.6 g, 20 mmol) in 10 mL of $CH_2Cl_2$ and $Et_3N$ (2.4 g, 24 mmol) were added to a stirred solution of crude **3** base (4.0 g, 17 mmol) in 40 mL of $CH_2Cl_2$ at 0–5 °C. After 5 min the reaction was warmed to room temperature and stirred for 16 h. The $CH_2Cl_2$ solution was extracted with 5 N HCl, 3 N $NH_4OH$, and saturated NaCl solution, and dried over $Na_2SO_4$, and the solvent was removed in vacuo to give a pale yellow oil. Crystallization from EtOAc–hexane gave 1.1 g (23%) of white crystals: mp 65–67 °C (anal. sample, mp 80–105 °C); NMR ($CDCl_3$) $\delta$ 4.07 (br, 1 H, NCH), 2.65 (m, 2 H, Ar $CH_2$), 1.86 (s, 3 H, $COCH_3$), 1.10–1.80 (m, 6 H, $CH_2CH_2CH_2$); TLC $R_f$ 0.37 (silica gel G; acetone–ether, 1:20). Anal. ($C_{16}H_{23}NO_3$) C, H, N.

***trans*-N-Acetyl-2-(3,4-dimethoxybenzyl)cyclopentylamine (6).** Compound **6** was synthesized from **4** (as above) in 16% yield: white crystals, from EtOAc–hexane; mp 103–105 °C (anal. sample, mp 106–107 °C); NMR ($CDCl_3$) $\delta$ 4.42 (br, 1 H, NCH), 1.98 (s, 3 H, $COCH_3$), 1.24–1.82 (m, 8 H, Ar $CH_2$, $CH_2CH_2CH_2$); TLC $R_f$ 0.34 (silica gel G; acetone–ether, 1:20). Anal. ($C_{16}H_{23}NO_3$) C, H, N.

**Cardiovascular Experiments.** Forty mongrel dogs of both sexes with an average weight of 10 kg (range 3.5–20 kg) were injected with morphine sulfate (5 mg/kg) and anesthetized with sodium pentobarbital (20 mg/kg iv). Surgical anesthesia, as evidenced by lack of corneal reflex, was maintained with additional barbiturate (3–4 mg/kg) as necessary. The animals were intubated endotracheally, and the right femoral artery and vein were cannulated. All injections thereafter were made through the venous cannula. Injection volumes were adjusted to 2.0 mL/10 kg and followed by 2–3 mL of 0.9% saline containing 10 units of heparin/mL. Arterial blood pressure was recorded with an RP 1500 pressure transducer and a desk-top model (DMP-4B) physiograph. Mean arterial blood pressure was calculated as diastolic blood pressure plus one-third pulse pressure. At the start of each experiment, atropine (1 mg/kg) was given to eliminate vagal control of heart rate. Autonomic nervous system responsivity was tested with norepinephrine (0.1 $\mu$g/kg), isoproterenol (0.1 $\mu$g/kg), and dopamine (3–20 $\mu$g/kg). The catecholamine solutions contained ascorbic acid (0.02%) as antioxidant.

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# Synthesis and Orexigenic Activity of Some 1-Methyl-4-piperidylidene-Substituted Pyrrolo[2,1-*b*][3]benzazepine and Dibenzocycloheptene Derivatives

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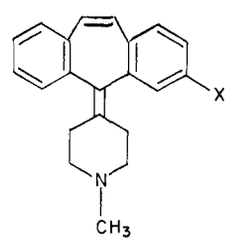
The synthesis and orexigenic activity of some unsubstituted and *Bz*-carboxylic acid substituted 1-methyl-4-piperidylidenepyrrolo[2,1-*b*][3]benzazepine and dibenzocycloheptene derivatives are described. 10,11-Dihydro-3-carboxycyproheptadine (**7c**) has been selected for clinical evaluation as an orexigenic agent based on its low threshold dose for increasing food consumption in cats (0.031 mg/kg po) and its lack of undesirable central nervous system activity. The levorotatory enantiomer of 3-carboxycyproheptadine (**1d**) and the 9-carboxypyrrolobenzazepine derivative **4f** also possess orexigenic activity, but with these compounds such activity diminishes sharply below 0.25 mg/kg po. The unsubstituted 1-methyl-4-(5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ylidene)piperidine (**4d**) and its 6,11-dihydro analogue (**4a**) are comparable to cyproheptadine (**1a**) in promoting hyperphagia in cats.

One of the more useful clinical attributes of the antihistaminic–antiserotonin drug cyproheptadine (**1a**) is



**1a**, X = H
**b**, X = $OCH_3$
**c**, X = $CO_2C_2H_5$
**d**, X = $CO_2H$

stimulation of appetite with a concomitant increase in food consumption (hyperphagia) and gain in total body weight.[1] Accordingly, **1a** has been used to promote appetite and weight gain in both children and adults with essential anorexia,[2,3] in children with pulmonary tuberculosis or chronic pulmonary conditions,[4] in patients with chronic hepatic diseases,[5] in individuals suffering from anorexia nervosa,[6-8] and in those patients having a generally debilitated condition.[9]

The levorotatory (absolute configuration $pR_apS_b$) but not the dextrorotatory enantiomer of 3-methoxycyproheptadine (**1b**) has also been reported to possess

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Table I. Food Consumption[a]

| compd | dose, mg/kg po | av grams consumed ± SD:[b] control day/test day | | |
|---|---|---|---|---|
| | | 30 min | 60 min | 180 min |
| (+)-1d | 0.50 | 71 ± 13/68 ± 22 | 94 ± 19/96 ± 17 | 125 ± 16/141 ± 25[c] |
| | 0.25 | 68 ± 32/66 ± 42 | 86 ± 31/91 ± 44 | 137 ± 41/138 ± 48 |
| (−)-1d | 0.50 | 72 ± 35/108 ± 32[c] | 102 ± 33/124 ± 36[c] | 149 ± 36/188 ± 49[c] |
| | 0.25 | 62 ± 17/76 ± 16 | 90 ± 25/109 ± 18[c] | 133 ± 30/169 ± 26[c] |
| (±)-1d | 0.50 | 116 ± 30/147 ± 32[c] | 160 ± 34/203 ± 35[c] | 219 ± 34/273 ± 42[c] |
| | 0.25 | 108 ± 24/129 ± 22[c] | 147 ± 31/179 ± 39[c] | 191 ± 25/236 ± 39[c] |
| 4a·$C_2H_2O_4$[d] | 0.50 | 117 ± 39/204 ± 60[c] | 137 ± 35/219 ± 55[c] | 166 ± 32/234 ± 49[c] |
| | 0.25 | 91 ± 38/175 ± 29[c] | 124 ± 39/212 ± 42[c] | 175 ± 50/239 ± 41[c] |
| 4c·HCl[e] | 0.50 | 92 ± 33/109 ± 36 | 125 ± 45/142 ± 32 | 173 ± 43/193 ± 30 |
| | 0.25 | NT[f] | NT[f] | NT[f] |
| 4d·$C_2H_2O_4$[d] | 0.50 | 133 ± 51/189 ± 49[c] | 148 ± 44/217 ± 41[c] | 193 ± 46/243 ± 33[c] |
| | 0.25 | 113 ± 33/172 ± 20[c] | 134 ± 40/208 ± 37[c] | 183 ± 46/239 ± 37[c] |
| 4f·HCl[e] | 0.50 | 78 ± 24/93 ± 24[c] | 114 ± 23/129 ± 28[c] | 170 ± 35/194 ± 45[c] |
| | 0.25 | 73 ± 37/98 ± 31[c] | 112 ± 46/128 ± 39[c] | 176 ± 40/210 ± 52[c] |
| 7c·HCl[e] | 0.50 | 84 ± 38/105 ± 49 | 102 ± 42/155 ± 67[c] | 134 ± 45/221 ± 84[c] |
| | 0.25 | 68 ± 20/89 ± 32[c] | 102 ± 26/127 ± 18[c] | 145 ± 30/170 ± 15[c] |
| cyproheptadine (1a) | 0.50 | 135 ± 47/190 ± 63[c] | 157 ± 50/221 ± 50[c] | 194 ± 50/256 ± 35[c] |
| | 0.25 | 109 ± 34/165 ± 34[c] | 129 ± 35/200 ± 41[c] | 179 ± 45/231 ± 52[c] |
| methylcellulose | | | | 181 ± 40/195 ± 33 |
| | | | | 210 ± 39/198 ± 41 |
| | | | | 195 ± 55/184 ± 52 |

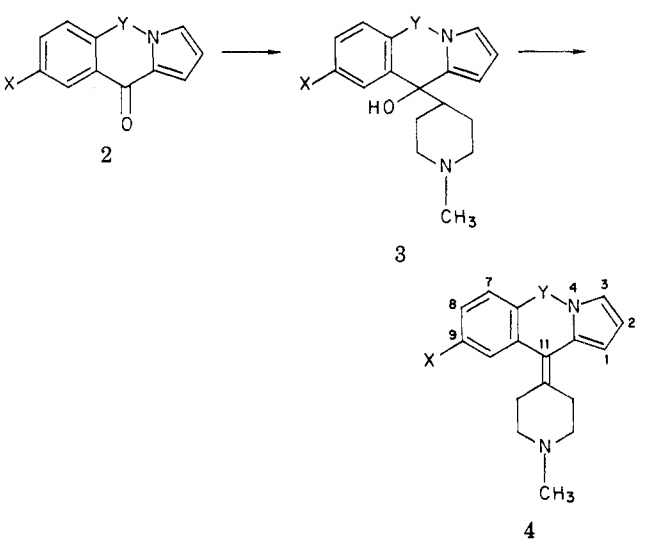
[a] See Experimental Section for a description of the pharmacological testing. [b] Each compound, except 4c, was tested at two dose levels, 0.50 and 0.25 mg/kg, using 10 cats per dose level. [c] Represents a significant increase in food consumption, $p < 0.05$ (two-tailed paired Student's $t$ test). [d] Hydrogen oxalate salt. [e] Hydrochloride salt. [f] Not tested at this lower dose.

orexigenic activity.[10] In this case, however, the introduction of the nuclear substituent into the cyproheptadine nucleus also confers potent central antidopaminergic activity to the molecule, and, indeed, this latter activity also resides solely in the levorotatory enantiomer.[11] Thus, unlike **1a** which has no notable central nervous system activity,[12] **1b** could have undesired central nervous system activity if used as an orexigenic agent.

Recently, the synthesis of a series of 1-methyl-4-(6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ylidene)-piperidine and 1-methyl-4-(5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ylidene)piperidine derivatives having lipophilic nuclear substituents in the 9 position of the tricyclic nucleus has been reported.[13a] These compounds are potent antidopaminergic agents.[13b] In this regard, then, the nuclear substituted pyrrolobenzazepines are similar to nuclear substituted cyproheptadine derivatives.[11]

We now report that the parent pyrrolobenzazepine compounds **4a** and **4d** resemble **1a** in their ability to stimulate appetite and cause an increase in food consumption in cats. Further, we report that the carboxylic acid **4f**, derived from the corresponding nitrile **4e**, retains this ability to promote food consumption, yet no longer possesses the antidopaminergic activity seen in its precursor.[13b] This latter observation has, therefore, prompted the preparation of the carboxylic acid derivative of 10,11-dihydrocyproheptadine (**7c**) and of the enantiomers of (±)-3-carboxycyproheptadine[14] [(±)-**1d**] for testing as potential orexigenic agents.

Scheme I[a]




[a] For **2**, **3**, and **4**: a, Y = $CH_2CH_2$, X = H; **b**, Y = $CH_2CH_2$, X = CN; c, Y = $CH_2CH_2$, X = $CO_2H$; d, Y = CH=CH, X = H; e, Y = CH=CH, X = CN; f, Y = CH=CH, X = $CO_2H$.

**Chemistry.** The unsubstituted pyrrolobenzazepines **4a** and **4d**, as well as the bromo compound **7a**, were prepared by addition of 1-methyl-4-piperidylmagnesium chloride to the appropriate ketones,[15a-c] followed by dehydration of the resulting tertiary carbinols **3a**, **3d**, and **6**, respectively. The nitrile derivative **7b** was prepared from the corre-

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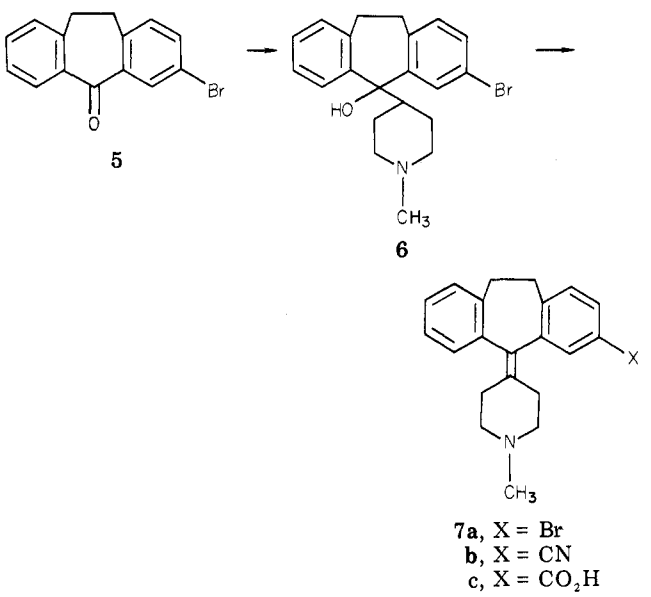
Table II. Food Consumption[a]

| compound | dose, mg/kg po | av grams consumed ± SD:[b] control day/test day | | |
|---|---|---|---|---|
| | | 30 min | 60 min | 180 min |
| (−)-1d | 0.063 | 68 ± 17/57 ± 28 | 94 ± 18/98 ± 34 | 159 ± 17/166 ± 44 |
| | 0.031 | 68 ± 20/55 ± 26 | 95 ± 17/79 ± 36 | 157 ± 27/159 ± 38 |
| 4a·$C_2H_2O_4$ | 0.063 | 52 ± 13/120 ± 41[c] | 74 ± 22/144 ± 50[c] | 133 ± 50/190 ± 63[c] |
| | 0.016 | 77 ± 21/142 ± 37[c] | 106 ± 31/168 ± 41[c] | 159 ± 45/215 ± 32[c] |
| 4d·$C_2H_2O_4$ | 0.063 | 66 ± 28/137 ± 46[c] | 100 ± 37/178 ± 44[c] | 166 ± 62/219 ± 31[c] |
| | 0.016 | 43 ± 16/91 ± 35[c] | 69 ± 16/119 ± 42[c] | 126 ± 33/182 ± 45[c] |
| 4f·HCl | 0.031 | 55 ± 25/67 ± 29 | 84 ± 25/105 ± 28 | 145 ± 34/172 ± 49[c] |
| | 0.031 | 65 ± 18/88 ± 27[c] | 98 ± 9/113 ± 30 | 184 ± 52/182 ± 48 |
| 7c | 0.063 | 88 ± 33/122 ± 37[c] | 118 ± 32/138 ± 33 | 174 ± 26/204 ± 33[c] |
| | 0.031 | 53 ± 20/75 ± 26[c] | 83 ± 14/95 ± 21[c] | 126 ± 24/152 ± 32[c] |
| | 0.016 | 97 ± 25/104 ± 16 | 139 ± 30/137 ± 21 | 180 ± 39/190 ± 28 |
| cyproheptadine (1a) | 0.063 | 56 ± 14/112 ± 54[c] | 80 ± 28/130 ± 44[c] | 134 ± 59/195 ± 62[c] |
| | 0.016 | 75 ± 35/118 ± 32[c] | 108 ± 41/160 ± 58[c] | 157 ± 46/193 ± 49[c] |

[a] See Experimental Section for a description of the pharmacological testing. [b] Each compound was tested at the dose level indicated using 10 cats each time. [c] Represents a significant increase in food consumption, $p < 0.05$ (two-tailed paired Student's $t$ test).

Scheme II




sponding bromo compound by reaction with cuprous cyanide in refluxing dimethylformamide.[16] Because of the known acid sensitivity of the pyrrole nucleus, basic hydrolysis of the nitriles **4b** and **4e** to their respective carboxylic acids **4c** and **4f** was employed (Scheme I). The nitrile **7b**, however, was hydrolyzed to **7c** in refluxing 6 N hydrochloric acid (Scheme II). Resolution of (±)-**1c** was effected using the procedure described previously for the resolution of **1b**.[10] The resulting enantiomeric esters then were saponified under mild conditions to give the enantiomeric acids (+)-**1d** and (−)-**1d**.

## Pharmacological Results and Discussion

As seen from the data in Table I, the parent pyrrolobenzazepines **4a** and **4d**, as well as the carboxylic acids (−)-**1d**, **4f**, and **7c**, showed orexigenic activity in cats at both the 0.50 and 0.25 mg/kg po dose levels. The dihydro acid **4c** was inactive at the higher of these two dose levels and was not tested further. That the orexigenic activity of (±)-**1d** resides in the levorotatory enantiomer (−)-**1d** is evident from the data of Table I, where an increase in food consumption at both 0.50 and 0.25 mg/kg po is seen to occur with (−)-**1d** but not with (+)-**1d**. Follow-up testing of (−)-**1d** at 0.063 and 0.031 mg/kg po and **4f** at 0.031 mg/kg po (Table II) showed no activity for the former compound and only marginal activity for the latter compound. In contrast, **4a**, **4d**, and **7c** showed consistent increases in food consumption at the 0.063 mg/kg po dose level. The threshold dose for orexigenic activity of **7c** appears to be at the 0.031 mg/kg po dose level, since below that dose no hyperphagia was observed. The unsubstituted pyrrolobenzazepines **4a** and **4d** resemble **1a** in that at the lowest dose tested, 0.016 mg/kg po, the compounds still promoted an increase in food consumption.

On the basis of additional data on the appetite-stimulating activity of **7c**,[17] together with a study of its other pharmacological attributes,[17] **7c** has been selected for evaluation in humans as an orexigenic agent.

## Experimental Section

Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Optical rotation measurements were determined with a Perkin-Elmer 141 automatic polarimeter. At least two readings were recorded at each wavelength and showed a deviation of ±0.005°. NMR spectra were recorded on a Varian T-60 spectrometer, employing $(CH_3)_4Si$ as an internal standard, and are consistent with the assigned structures. All compounds were homogeneous by thin-layer chromatographic analysis. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

**Resolution of (±)-1-Methyl-4-(3-carbethoxy-5*H*-dibenzo[*a*,*d*]cycloheptene-5-ylidene)piperidine [(±)-1c] and Saponification to the Chiral Acids (−)-1d and (+)-1d. Levorotatory Isomer (−)-1d.** To a solution of 5.00 g (0.0139 mol) of (±)-**1d** in 50 mL of ethanol was added 5.38 g (0.0139 mol) of di-*p*-toluoyl-*d*-tartaric acid in 50 mL of ethanol. The crystalline precipitate that formed on cooling was removed by filtration, washed with ethanol, collected, and dried to give 3.90 g of crystalline salt. Two recrystallizations of this salt from ethanol gave a product having a constant rotation: $[\alpha]^{25}_{589}$ −165°, $[\alpha]^{25}_{578}$ −176°, $[\alpha]^{25}_{546}$ −211°, $[\alpha]^{25}_{436}$ −523° (*c* 0.74, pyridine). This salt was converted to the free base (−)-**1c** using sodium bicarbonate solution and extracting it into ether. The ether phase was washed with water, dried ($MgSO_4$), and filtered, and the solvent was removed in vacuo to afford 1.50 g of pure (−)-**1c**: mp 94–96 °C; $[\alpha]^{25}_{589}$ −207°, $[\alpha]^{25}_{578}$ −220°, $[\alpha]^{25}_{546}$ −268°, $[\alpha]^{25}_{436}$ −728° (*c* 0.89, $CHCl_3$). A solution of 1.24 g of (−)-**1c** in 55 mL of methanol containing 4.12 mL of 2 N KOH was stirred at room temperature for 7 days. The methanol was removed in vacuo at 25 °C, and the residue

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was dissolved in a minimum amount of water. The clear aqueous solution was acidified to pH 6 with glacial acetic acid, and the precipitate that formed was removed by filtration, washed with water, and dried to give 1.08 g of (−)-**1d**: mp 300–305 °C; $[\alpha]^{25}_{589}$ −180°, $[\alpha]^{25}_{578}$ −194°, $[\alpha]^{25}_{546}$ −239°, $[\alpha]^{25}_{436}$ −675° (*c* 0.50, 0.1 N HCl); NMR ($CF_3CO_2D$) δ 2.7–3.6 (m, 12 H, aliphatic CH, $CO_2H$), 7.05 (d, $J$ = 2 Hz, 2 H, vinyl CH), 7.2–8.0 (m, 7H, Ar H). Anal. ($C_{22}H_{21}NO_2$) C, H, N.

**Dextrorotatory Isomer (+)-1d.** Starting with 4.08 g (0.0114 mol) of (±)-**1d** in 20 mL of hot ethanol and 4.60 g (0.0114 mol) of di-*p*-toluoyl-*l*-tartaric acid monohydrate in 20 mL of ethanol and using the procedure as described above, 2.10 g of crystalline salt was obtained: $[\alpha]^{25}_{589}$ +162°, $[\alpha]^{25}_{578}$ +172°, $[\alpha]^{25}_{546}$ +206°, $[\alpha]^{25}_{436}$ +509° (*c* 0.77, pyridine). Conversion to the free base and crystallization from acetonitrile gave (+)-**1c**: mp 95–96.5 °C; $[\alpha]^{25}_{589}$ +208°, $[\alpha]^{25}_{578}$ +221°, $[\alpha]^{25}_{436}$ +728° (*c* 0.93, $CHCl_3$). A solution of 0.75 g of (+)-**1c** in 35 mL of methanol containing 2.5 mL of 2.5 N KOH was warmed at 50 °C for 15 min and then was stirred at room temperature overnight. The methanol was removed on a rotary evaporator, and the residue was dissolved in water. The clear aqueous solution was acidified with glacial acetic acid, and the precipitate that formed was removed by filtration and dried to afford 0.67 g of (+)-**1d**: mp 300–306 °C; $[\alpha]^{25}_{589}$ +178°, $[\alpha]^{25}_{578}$ +189°, $[\alpha]^{25}_{546}$ +232°, $[\alpha]^{25}_{436}$ +658° (*c* 0.52, 0.10 N HCl); NMR spectrum was identical with the NMR spectrum of (−)-**1d**. Anal. ($C_{22}H_{21}NO_2$) C, H, N.

**1-Methyl-4-(6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ylidene)piperidine (4a) Hydrogen Oxalate.** To a solution of 7.0 g (0.036 mol) of 6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-one (**2a**) in 100 mL of THF was added 200 mL of a 0.43 M solution of 1-methyl-4-piperidinylmagnesium chloride in THF. After the addition was complete, water (40 mL) was added, and the mixture then was diluted with methylene chloride. The organic phase was separated, dried ($MgSO_4$), filtered, and concentrated to dryness. The residue was chromatographed on a silica gel column (3.8 × 43 cm) using 5% (v/v) methanol in $CHCl_3$. Combination of the appropriate fractions and evaporation of the solvent afforded 7.3 g (68%) of 11-hydroxy-11-(1-methylpiperidin-4-yl)-6,11-dihydro-5*H*-pyrrolo[2,1-*b*][3]benzazepine (**3a**), mp 175–177 °C. Anal. ($C_{19}H_{24}N_2O$) C, H, N.

A solution of 2.0 g of **3a** and 0.75 g of oxalic acid in 100 mL of ethanol was stirred and refluxed for 18 h. On cooling, the hydrogen oxalate salt of **4a** crystallized. This material was collected by filtration, washed with ethanol, and dried to give 2.15 g of **4a**·$C_2H_2O_4$, mp 238–243 dec. Anal. ($C_{19}H_{22}N_2$·$C_2H_2O_4$) C, H, N.

**1-Methyl-4-(5*H*-pyrrolo[2,1-*b*][3]benzazepin-11-ylidene)piperidine (4d) Hydrogen Oxalate.** In a manner similar to that described for the preparation of **3a**, ketone **2d** (0.40 g) was treated with 1-methyl-4-piperidylmagnesium chloride to afford 0.47 g (78%) of **3d**, mp 151–153 °C. Anal. ($C_{19}H_{22}N_2O$) C, H, N.

A solution of 2.7 g of **3d** in 100 mL of $CHCl_3$ was treated with HCl (g) for several minutes, at which time the solution changed color. The solution was poured into water, and the organic phase was removed, washed with 5% sodium carbonate solution, and dried ($MgSO_4$). The crude product was purified by chromatography on silica gel using 5% methanol in $CHCl_3$. The 2.3 g of **4d** thus obtained was treated with a solution of oxalic acid in ethanol to afford 2.2 g of **4d**·$C_2H_2O_4$, mp 222 °C dec. Anal. ($C_{19}H_{20}N_2$·$C_2H_2O_4$) C, H, N.

**11-(1-Methyl-4-piperidylidene)-5*H*-pyrrolo[2,1-*b*][3]benzazepine-9-carboxylic Acid (4f) Hydrochloride.** 9-Cyano-11-(1-methyl-4-piperidylidene)-5*H*-pyrrolo[2,1-*b*][3]benzazepine (**4e**; 2.0 g, 0.0066 mol) was dissolved in 55 mL of 90% aqueous ethanol containing 1.1 g (0.02 mol) of KOH, and the solution was refluxed for 3 days. The ethanol was removed in vacuo, the residue was dissolved in 120 mL of water, and the aqueous solution was washed twice with a 1:1 ether–benzene mixture. The aqueous phase then was acidified with glacial HOAc to pH 6, and the resulting suspension was concentrated to half-volume in vacuo. The resulting beige solid was collected by filtration and was washed with water and then with acetone to afford 1.6 g (74%) of **4f**, mp 208–215 °C. The hydrochloride salt of **4f** was prepared using ethanolic HCl and was recrystallized from a mixture of 35 mL of acetonitrile and 1 mL of water to yield 1.3 g of pure **4f**·HCl, mp 214 °C dec. Anal. ($C_{20}H_{20}N_2O_2$·HCl) C, H, Cl, N.

**6,11-Dihydro-11-(1-methyl-4-piperidylidene)-5*H*-pyrrolo-[2,1-*b*][3]benzazepine-9-carboxylic Acid (4c) Hydrochloride.** Starting with 1.2 g (0.0039 mol) of **4b** in 20 mL of EtOH containing 2 mL of 20% aqueous NaOH and using the procedure as described for the preparation of **4f**, 0.82 g of **4c** was obtained, mp dec from 265 °C. The hydrochloride salt of **4c** was prepared and recrystallized from EtOH–$Et_2O$, mp dec from 224 °C. Anal. ($C_{20}H_{22}N_2O_2$·HCl·0.25$H_2O$) C, H, Cl, N.

**1-Methyl-4-(3-cyano-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine (7b).** To an ice-cooled solution of 15.0 g (0.0523 mol) of **5** in 150 mL of THF was added dropwise over 0.5 h 100 mL of 0.53 M 1-methyl-4-piperidylmagnesium chloride in THF. The solution was stirred for 1 h, and then the THF was removed on a rotary evaporator. The residue was dissolved in benzene, and water was added dropwise until a clear benzene supernatant and a gelatinous aqueous phase was obtained. The organic phase was decanted, and the residue was extracted with 2–100 mL portions of hot benzene. The combined benzene phases were washed with water, and the solvent was removed. The residue crystallized when triturated with acetonitrile to afford, after filtration, 9.66 g (65%) of **6**, mp 203–207 °C. A mixture of 9.66 g of **6** and 130 mL of 6 N HCl was stirred and refluxed for 0.5 h. The bulk of the hydrochloric acid was removed under reduced pressure, and the residue was partitioned between 5% aqueous sodium hydroxide and ether. The ether phase was washed with water, dried ($MgSO_4$), and filtered, and the ether was evaporated to give 9.17 g of **7a**. A mixture of **7a** (9.17 g, 0.0249 mol), cuprous cyanide (4.58 g, 0.05 mol), and DMF (30 mL) was stirred and heated under reflux for 6.5 h. To the cooled solution was added 54 mL of water, 27 mL of a saturated sodium cyanide solution, and 75 mL of benzene. The mixture was stirred until a clear two-phase system was obtained. The benzene phase was removed, and the aqueous phase was extracted with 2–75 mL portions of benzene. The combined benzene phases were washed with 100 mL of dilute sodium cyanide solution and water and then dried over $MgSO_4$. After the solution was filtered, removal of the benzene gave 7.40 g of crystalline residue. This material was dissolved in $CHCl_3$ and passed over an alumina column (2.5 × 38 cm). The product was eluted with $CHCl_3$ to give 4.91 g of material. Recrystallization from isopropyl alcohol gave 4.00 g of pure **7b**, mp 152–154 °C. Anal. ($C_{22}H_{22}N_2$) C, H, N.

**1-Methyl-4-(3-carboxy-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-ylidene)piperidine (7c) Hydrochloride.** A mixture of 1.0 g (0.0032 mol) of **7b** and 20 mL of 6 N HCl was stirred and refluxed for 18 h. After cooling, the mixture was filtered, and the collected solid was washed with 6 N HCl and then with EtOH. The dried material weighed 1.03 g (87%). Recrystallization from EtOH gave pure **7c**·HCl, mp 304–307 °C. Anal. ($C_{22}H_{23}NO_2$·HCl) **C**, H, Cl, N.

**Pharmacology.** Orexigenic activity was evaluated by an increase in food consumption in cats. Adult male cats, individually caged with water available ad libitum, were allowed to eat for only 3 h daily (at the same time each day). The animals were maintained on this feeding schedule for at least 4 weeks prior to testing. A preweighed test meal (Science Diet Feline Ration, Riviana Foods, Inc.) was presented to each cat, and after 30, 60, and 180 min, the amount consumed was determined by reweighing the remaining food. An amount of food was presented which ensured a surplus, thus allowing unrestricted intake during the 3 h feeding period. Food eaten on the test (drug) day was compared with the amount consumed on the immediately preceding (control) day. Test compounds or a placebo dose of 1% methylcellulose was administered by gavage 30 min preceding the presentation of the test meal. No cat was given a test compound more often than once weekly. The compounds were suspended in 1% methylcellulose prior to administration. Each compound was tested at the dose level indicated using ten cats per dose.

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