desired base, mp 130–133 °C. After recrystallization from EtOH, the base (69) melted at 130–132 °C.

**1-[[2-[(2-Hydroxyethyl)amino]ethyl]amino]-6-hydroxy-4-methylthioxanthenone (72).** A solution of 1.0 g of 1-chloro-6-methoxy-4-methylthioxanthenone in 10 mL of acetic acid and 10 mL of 48% HI was refluxed for 2 h and then allowed to stand overnight. After two crystallizations from acetic acid, the 6-hydroxythioxanthenone (67) melted at 229–231 °C. Anal. ($C_{14}H_9ClO_2S$) C, H.

A suspension of 1.3 g of the above 6-hydroxythioxanthenone in 13.0 mL of *N*-(2-hydroxyethyl)ethylenediamine and 13.0 mL of pyridine was refluxed for 16 h. $H_2O$ was added to the cooled mixture, which was then set up to distill, and about 35 mL of distillate was collected. After cooling, the solid was collected by filtration and crystallized three times from EtOH to give the desired base: yield 1.0 g; mp 193–195 °C.

**Determination of Melting Temperatures of Drug–DNA Complexes.** All solutions used were prepared in a low ionic strength buffer of $3.3 \times 10^{-4}$ M $Na_2HPO_4$, $10^{-4}$ M sodium ethylenediaminetetraacetate, and $3 \times 10^{-3}$ M NaCl at pH 6.8. The DNA solution concentration was approximately 20 μg/mL of calf thymus DNA (Sigma type 1). The exact concentration was determined spectrophotometrically.[21] Several milligrams of the drugs to be tested were weighed accurately and dissolved in 10 mL of the buffer solution. Varying volumes of the drug solutions ranging from 20 to 200 μL were added to 2.0-mL aliquots of the DNA solution so that the final drug concentrations ranged from 2 to 20 μmol/L.

The drug–DNA solutions were degassed at 50 °C under vacuum (20 torr) and placed in a water-jacketed cuvette of a Beckmann DB-G grating spectrophotometer. The temperature of the solution was raised at a rate of 1 °C/min, while absorbance was being read at 2 °C intervals at 260 nm. The results were plotted ($A_{260nm}$ vs. temperature), and the $T_m$ was taken as the midpoints of the curve between the high and low temperature constant-absorbance regions. Under these conditions the $T_m$ of the uncomplexed DNA was 57.2 °C. Assuming that maximum intercalation occurs at a ratio of one drug molecule for every two base pairs, then at DNA concentrations of 20 μg/mL the maximum drug concentration for intercalation is 14.4 μmol/L. Beyond this limiting value, the drug does not intercalate but may bind electrostatically to phosphate residues. The secondary binding may cause a slight increase in the $T_m$ of the drug–DNA complex. A series of $T_m$ determinations were made at different drug–DNA ratios, and the $T_m$ values were plotted vs. drug concentration (μmol/L). The $T_m$ values reported in Table III are those read off at drug concentrations of 14.4 μmol/L or the point where the slope of the curve changed abruptly below this concentration.

**Determination of Drug–DNA Association Constants.** All solutions were prepared in a 0.009 M Tris–0.01 M NaCl buffer at pH 7.0. A crude DNA solution was prepared by dissolving 100 mg of the calf thymus DNA in 50 mL of buffer and dialyzing against 200-mL quantities of 4, 3, 2, and 1 M NaCl buffer and 0.1 M NaEDTA, and finally four times against the Tris buffer. After dialysis, the DNA solution was diluted to 100 mL with Tris buffer and frozen. Each week a new DNA portion was thawed, and the concentration was determined spectrophotometrically.[21]

Aliquots, 10 to 200 μL, of the DNA solution were added sequentially to 5 mL of a $5 \times 10^{-5}$ M drug solution at room temperature. After equilibration, absorption at 448 nm was determined on a Gilford 240 single-beam spectrophotometer. Approximately 15 aliquots were added per run so that about 1 mL of DNA solution was added per 5 mL of drug solution. The results were plotted and $K_{app}$'s calculated as described by Double and Brown[7] and are recorded in Table III.

**Acknowledgment.** We are indebted to the National Cancer Institute of the National Institutes of Health for a grant (CA-19674) which supported most of the work reported here and also for the results of the antitumor tests.

(21) L. M. Angerer and E. M. Mourdrianakis, *J. Mol. Biol.*, **63**, 505 (1972).

# Synthesis and Peripheral Cardiovascular Action of *cis*- and *trans*-2-(3,4-Dimethoxybenzyl)cyclopentylamine Hydrochlorides

Sonia R. Teller* and Charles H. Jarboe

*Department of Pharmacology and Toxicology, School of Medicine, University of Louisville, Louisville, Kentucky 40292.*
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The hydrochlorides of *cis*- and *trans*-2-(3,4-dimethoxybenzyl)cyclopentylamine have been synthesized. They are transient hypotensive agents with early and delayed depressor effects and antagonists of dopamine-induced vasodepression. In the atropinized and phenoxybenzamine-treated dog, the threshold dose for hypotension was 3–5 μmol/kg. The early depressor phases were attenuated variably by different types of antagonists, suggesting a nonspecific interaction with blood pressure regulation mechanisms. Cimetidine blocked the delayed depressor phases, consistent with endogenous histamine release. The cis amine hydrochloride was three to four times more potent than its trans isomer as a peripheral dopamine blocking agent. Cimetidine but not diphenhydramine interfered with this effect.

Dopamine cardiovascular pharmacology is of particular interest. The compound causes vasodepression in response to action at specific vascular receptors.[1,2] Vasodilation from inhibition of autonomic ganglionic transmission is attributed to specific dopamine receptors in sympathetic ganglia and postganglionic nerves.[3-5] The interaction of dopamine with α- and β-adrenergic receptors is also well documented,[1-3] and it has been postulated that there is a composite dopamine–serotonin receptor in the canine vasculature.[6]

In the central nervous system, dopamine is of significant importance in modulating motor, behavioral, and neuroendocrine functions. Dopamine agonists and antagonists have been used therapeutically in those diseases that involve either its apparent deficiency or superabundance.[7] Several types of dopamine-sensitive sites and receptors have been identified by specific radioligand binding assays and by correlation with biological response patterns to dopaminergic drugs.[8] Evidence favors the existence of

(1) L. I. Goldberg, *Pharmacol. Rev.*, **24**, 1 (1972).
(2) P. E. Setler, R. G. Pendleton, and E. Finlay, *J. Pharmacol. Exp. Ther.*, **192**, 702 (1975).
(3) L. I. Goldberg, P. H. Volkman, and J. D. Kohli, *Annu. Rev. Pharmacol. Toxicol.*, **18**, 57 (1978).
(4) S. Z. Langer, *Br. J. Pharmacol.*, **60**, 481 (1977).
(5) M. F. Lokhandwala and B. S. Jandhyala, *J. Pharmacol. Exp. Ther.*, **210**, 120 (1979).
(6) J. C. Gilbert and L. I. Goldberg, *J. Pharmacol. Exp. Ther.*, **193**, 435 (1975).
(7) J. R. Bianchine, G. M. Shaw, J. E. Greenwald, and S. M. Dandalides, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 2434 (1978).

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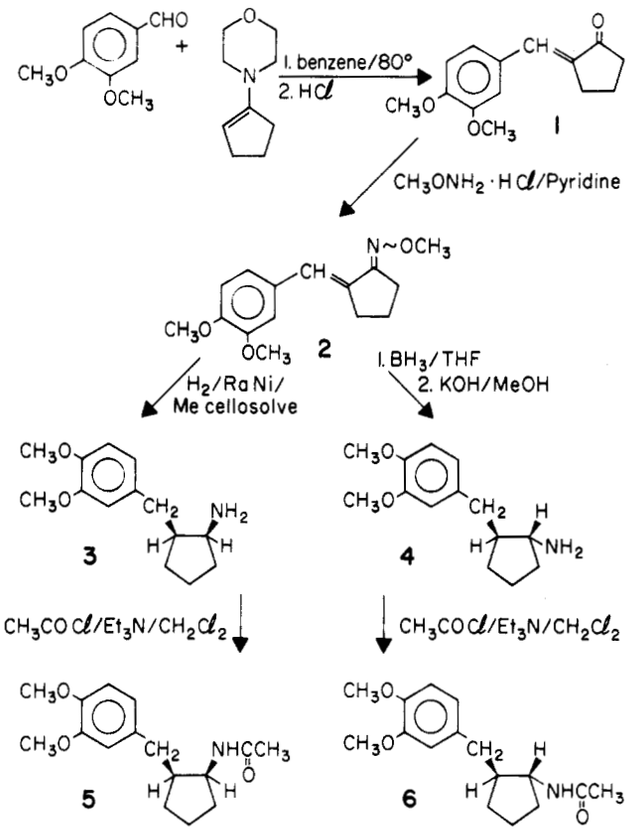
Scheme I




multiple central nervous system and peripheral dopamine receptors that differ in sensitivity to agonists and antagonists.[9,10]

We have been interested in compounds which differentiate between peripheral and central dopamine receptors and have shown 2,5-bis(3,4-dimethoxybenzyl)cyclopentylamine to be such an agent.[11] In contrast to its peripheral dopamine blocking activity, this compound potentiates response to the dopamine agonist apomorphine in the central nervous system. In a continuation of the work, we have modified this molecule by eliminating one 3,4-dimethoxybenzyl group. We report here the synthesis and peripheral pharmacological activity of the resulting diastereomeric alicyclic analogues, *cis*- and *trans*-2-(3,4-dimethoxybenzyl)cyclopentylamine (**3** and **4**).

**Chemistry.** The synthesis of compounds **3** and **4** is outlined in Scheme I. Benzaldehyde has been reported to condense with enamines to give 2-benzylidinecycloalkanones in good yields.[12] The similarly prepared substituted benzylidine derivative **1** had been previously prepared in unreported yield by condensation of cyclopentanone in alkali with veratraldehyde.[13] The oxime ether **2** was readily prepared by refluxing the unsaturated ketone with methoxyamine hydrochloride in pyridine. Catalytic hydrogenation of the oxime ether afforded **3** in good yield. Reduction of the oxime ether to **4** was by the method of Feuer and Braunstein.[14] The low yield was unexpected; however, no other compound could be isolated from the complex reaction mixture. Moreover, yields were lower when acidic conditions were employed for the hydrolysis of the organoborane intermediate. The isomeric nature of the two amines was evident from elemental analyses, melting points, IR and NMR spectra, and $R_f$ values by thin-layer chromatography.

Stereochemical assignments were confirmed by preparation of **5** and **6** by reaction of amines **3** and **4** with acetic anhydride in pyridine and by NMR characterization of the *N*-acetyl derivatives. Proton resonance frequency shifts in the NMR spectra of the cis and trans amides were consistent with these assignments.[15] Similar chemical shifts have been reported to occur with *cis*- and *trans*-arylcyclobutylacetamides.[16]

**Pharmacology.** Intravenous injections of dopamine exerted dose-related pressor and depressor effects on arterial mean blood pressure. A monophasic depressor response was elicited by a low dose (3 μg/kg) and is attributed to the action of dopamine at dopamine-specific cardiovascular receptors.[2] The depressor effect was not antagonized by atropine, β-adrenergic, or $H_1$- or $H_2$-histamine antagonists. Dopamine-induced vasodepression has been reported to be inhibited by bulbocapnine, haloperidol, and metoclopramide.[2,11] With doses of 6 to 20 μg/kg, a biphasic response was observed: an initial increase in mean blood pressure, followed by a more prolonged pressure reduction. The pressor response dominated the high dose range of 20 to 81 μg/kg and is attributed to the action of dopamine at α-adrenergic receptors.[1,2] After administration of phenoxybenzamine (5–10 mg/kg) over 30–60 min, the pressor response was eliminated, and only depressor responses were observed to doses of dopamine (3–81 μg/kg). Thus, monophasic depressor dose–response curves were generated without pressor effect interference. Compounds **3** and **4** were tested for dopamine antagonist activity in the same animals by their administration 2 min before each of a second series of dopamine injections (3–81 μg/kg). They were also tested for dose-dependent antagonism of the depressor response to 3 μg of dopamine/kg before and after the administration of phenoxybenzamine. Other drugs, tested as antagonists to the actions of **3** and **4**, were injected 10 to 20 min before each test compound. In addition to phenoxybenzamine, other standard antagonists used in this study were propranolol, metoclopramide, diphenhydramine, cimetidine, and methysergide.

The cis and trans isomers, **3** and **4**, produced a dose-dependent (3–100 μmol/kg) transient depression of mean blood pressure. This depression was maximal approximately 30 s after injection and lasted 20 s. This early depressor phase was not significantly altered by previous administration of phenoxybenzamine (5–10 mg/kg). The threshold dose for this effect was 3–5 μmol/kg and was determined from a linear plot of percent decrease of mean blood pressure vs. log dose. At 15 μmol/kg, the mean percent decreases in mean blood pressure caused by **3** was

(8) P. Seeman, *Pharmacol. Rev.*, **32**, 229 (1980).
(9) L. I. Goldberg and J. D. Kohli, *Commun. Psychopharmacol.*, **3**, 447 (1979).
(10) J. W. Kebabian and D. B. Calne, *Nature (London)*, **277**, 93 (1979).
(11) C. H. Jarboe, S. F. Lipson, M. J. Bannon, and D. A. Dunnigan, *J. Med. Chem.*, **21**, 1318 (1978).
(12) L. Birkofer, S. M. Kim, and H. D. Engels, *Chem. Ber.*, **95**, 1495 (1962).
(13) A. Maccioni and E. Marongiu, *Ann. Chim. (Rome)*, **49**, 1283 (1959).
(14) H. Feuer and D. M. Braunstein, *J. Org. Chem.*, **34**, 1817 (1969).
(15) Aromatic shielding phenomena due to the orientation of the cis $COCH_3$ and cis NCH protons above the plane of the phenyl ring cause these proton resonance signals to appear at higher resonance frequencies than their trans counterparts. Interaction of the *cis*-*N*-acetyl group with the aromatic ring deshields the benzylic methylene protons and causes the cis $CH_2$-Ar resonance signal to appear at a lower resonance frequency than that of the trans $CH_2$-Ar.
(16) J. F. Bossart, Ph.D. Dissertation, University Microfilms International, No. 77-31, 832 (1977).

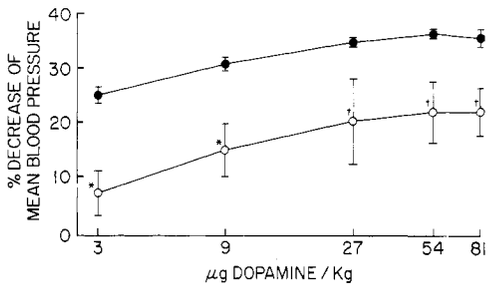



**Figure 1.** Compound **3** inhibition of dopamine blood pressure effects: (●) dopamine in the absence of drug; (○) dopamine 2 min after **3** (15 μmol/kg); (*) $p < 0.05$ significantly different from controls, paired Student's $t$ test, two tailed; (†) $p < 0.1$. Results are expressed as the mean ± SEM, $n = 4$.

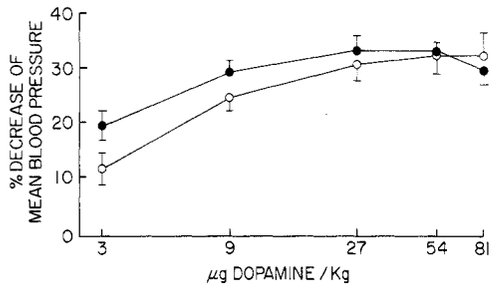



**Figure 2.** Compound **4** inhibition of dopamine blood pressure effects: (●) dopamine in the absence of drug; (○) dopamine 2 min after **4** (15 μmol/kg). $p > 0.2$ not significantly different from controls, paired Student's $t$ test, two tailed. Results are expressed as the mean ± SEM, $n = 3$.

30.0 ± 2.6 ($n = 7$); for **4** it was 25.1 ± 3.6 ($n = 7$). No lethality was observed with either **3** or **4** at doses up to 100 μmol/kg.

In phenoxybenzamine-treated animals, the early depressor phase of **3** and **4** was attenuated variably by several types of antagonists. Attenuation of the acute vasodepressor effects of a 15 μmol/kg dose of **4** approximated 80% after the administration of metoclopramide (5 mg/kg) or propranolol (1 mg/kg). Proportional decreases in the percent attenuation occurred with subsequent injections of **4** at 12-min intervals, suggesting a reversible pharmacological antagonism of the trans compound by these agents.

In contrast, attenuation of the early depressor phase of **3** (15 μmol/kg), by either metoclopramide (5 mg/kg) or propranolol (1 mg/kg), approximated 28%. Subsequent injections of **3** at 12-min intervals revealed that maximum attenuation occurred 30 to 40 min after administration of either blocking agent, suggesting a less specific, indirect interaction of these agents with the cis compound.

Methysergide (0.2 mg/kg) attenuated the early depressor phases of equimolar doses of **3** and **4** by 88%. In similar experiments, attenuation by cimetidine (1.5 mg/kg) of **3** and **4** approximated 34%.

The diversity of antagonists that block vasodepression by **3** and **4** is consistent with a combination of direct and indirect actions on the heart and blood vessels by the experimental compounds rather than from stimulation of one specific type of vascular receptor.

Both **3** and **4** attenuated the decrease in mean blood pressure produced by 3 μg of dopamine/kg. The threshold of **3** and **4** for this antagonism was 10 μmol/kg. However, **3** was three to four times more potent than was **4**. In both cases, antagonism of the dopamine depressor response was brief, usually less than 10 min. In the phenoxybenzamine-treated animals, after administration of 15 μmol/kg of **3**, the depression of mean blood pressure caused by dopamine was significantly shifted to the right ($p < 0.05$, $n = 4$) (Figure 1). In contrast, after equimolar injections of **4**, there was an insignificant shift of the dopamine dose–response curve ($p > 0.1$, $n = 3$) (Figure 2). The nature of this antagonism of dopamine exerted by **3** and **4** is prima facie evidence that the cis compound (**3**) is a competitive dopamine antagonist three to four times more active than its trans isomer (**4**).

Administration of 1.5 mg of cimetidine/kg did not alter mean blood pressure responses to dopamine at doses from 3 to 81 μg/kg. However, in the presence of cimetidine, the dopamine antagonism by **3** (at 15 μmol/kg) was greatly attenuated. Administration of 2 mg of diphenhydramine/kg did not attenuate dopamine antagonism by **3**. The weaker dopamine-antagonist activity of equimolar doses of **4** was completely abolished by cimetidine.

Several explanations are suggested by the unusual interference by cimetidine with the actions of **3** and **4**. Cimetidine may bind to a dopamine receptor and prevent **3** and **4** from binding. This would require that affinity of cimetidine for this receptor be less than that of dopamine but greater than that of **3** or **4**. Cimetidine could then be easily displaced by dopamine but not by **3** or **4** (affinity: DA ≫ cimetidine > **3** > **4**). The binding site could be considered a silent cimetidine receptor.

Secondly, **3** and **4** may bind to a site independent of the dopamine receptor and exert their action through allosteric antagonism. Cimetidine may interfere with the conformational transition induced by **3** and **4** at the allosteric site by (1) competing for the site or (2) by altering the conformation of a nearby region. In both cases, cimetidine could act without directly affecting the dopamine receptor.

In addition, the dopamine antagonism may require an intact histamine $H_2$ system. This mechanism would require (1) that **3** and **4** bind to a region that exposes an $H_2$ receptor to endogenous histamine, and (2) when the $H_2$ receptor contains histamine, then **3** and **4** can block dopamine's action. This $H_2$-histaminergic modulation of dopaminergic activity would then be inhibited in the presence of cimetidine. Evidence in support of the presence of $H_1$ and $H_2$ receptors mediating vasodilation in the peripheral vasculature has been reported.[17]

Besides the compounds' early depressor phase, a dose-related delayed depressor phase was observed for **3** and **4** in phenoxybenzamine-treated animals. The threshold dose for this effect was 15 μmol/kg. Approximately 1 min after injection, the mean blood pressure suddenly and rapidly declined, usually reaching its lowest point by 2 min. In comparable experiments, the percent decrease in mean blood pressure recorded 2 min after injection of 15 μmol/kg of **3** was 37.9 ± 2.7 ($n = 3$); for **4** it was 7.5 ± 6.3 ($n = 3$). A slow recovery to preinjection (base line) mean blood pressure was complete within 10 min. If five repetitive equimolar doses were given at 12–14 min intervals, a decrease in the intensity of the response ensued (Figure 3). No such tachyphylaxis was observed if equimolar doses were given at hourly intervals. This suggests that the compounds may be releasing some endogenous vasodepressor substance, such as histamine, which in turn is responsible for the delayed depressor phase. Depletion of readily mobilized tissue stores of the endogenous agent would account for the observed acute tolerance to the effect. In support of this, it was observed that if cimetidine was administered before **3** or **4**, (1) the delayed depressor response of **3** was substantially attenuated (70%) and (2) the delayed depressor of **4** was completely reversed to a

(17) P. Chipman and W. E. Glover, *Br. J. Pharmacol.*, **56**, 494 (1976).

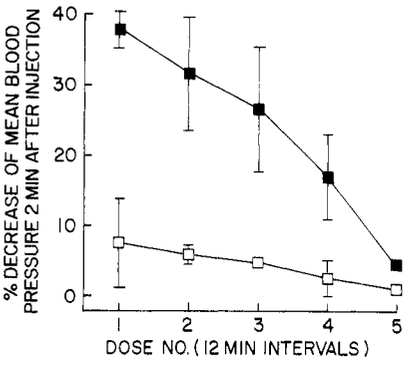



**Figure 3.** Effects of **3** and **4** on mean blood pressure 2 min after injection: (■) **3** (15 μmol/kg) ($n$ = 3); (□) **4** (15 μmol/kg) ($n$ = 3). Results are expressed as the mean ± SEM.

small pressor response (<5% increase in mean blood pressure).

These limited structure–activity studies have shown qualitative and quantitative differences between **3** and **4** with regard to their activity in the peripheral cardiovascular system. The complexity of their action is in marked contrast to the relatively simple peripheral dopamine blockade by 2,5-bis(3,4-dimethoxybenzyl)cyclopentylamine,[11] the model upon which the modified structures are based. Removal of one 3,4-dimethoxybenzyl group produced asymmetric molecules with less potency and shorter duration of action than their parent.[18] Perhaps because of its extended structure, the bis compound may have an increased affinity for peripheral dopamine receptor sites. Compounds **3** and **4**, with contracted structures and increased flexibility, appear to have less affinity for peripheral dopamine receptors and have capacity for interaction with other receptors as well. A unitary dopaminergic receptor model for the CNS has been proposed recently.[19] It contains subunits for high-affinity binding, with a 2:1 ratio for the number of antagonist vs. agonist sites. Using this model in the periphery, the bis compound could interact at two antagonist sites bridging an agonist site, more effectively blocking dopamine than the abbreviated derivatives.

The trans extended conformation of dopamine is postulated to be the active form for binding to dopamine receptors.[20,21] The trans β rotamer of dopamine is probably the preferred conformation for dopamine-induced vasodilation.[22] It would appear that certain internuclear distances between heteroatoms are necessary for activity of dopaminergic agonists and antagonists. Examination of Dreiding molecular models indicated that the nitrogen–oxygen distances in the cis amine were equal to those of the extended dopamine conformation and that those of the trans amine were not. The flexibility of all three molecules precludes exact definition of receptor spatial relationships. However, one explanation for the disparate effects of the cis and trans isomers in regard to their dopamine antagonism is the conformational similarity of the cis amine to the extended form of dopamine.

(18) The threshold dose of the bis compound which attenuated the depressor effect of 3 μg of dopamine/kg was 0.7–1.2 μmol/kg. Complete blockade of dopamine's effects occurred with 12–17 μmol of the bis compound/kg. Its duration of action was >18 min.
(19) J. E. Leysen, *Commun. Psychopharmacol.*, **3**, 397 (1979).
(20) D. D. Miller, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 2392 (1978).
(21) J. G. Cannon, *Adv. Neurol.*, **9**, 177–183 (1975).
(22) P. H. Volkman, J. D. Kohli, L. I. Goldberg, J. G. Cannon, and T. Lee, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 3602 (1977).

## Experimental Section

The enamine, 4-(1-cyclopentenyl)morpholine, was prepared by standard procedure[23] and fractionally distilled, bp 84–85 °C (0.5 mm) [lit.[23] bp 104–106 °C (12 mm)]. Melting points were determined using a Fisher-Johns apparatus and are uncorrected. Microanalyses were performed by the Spang Microanalytical Laboratory, Eagle Harbor, MI. IR spectra from Nujol mulls were obtained with a Perkin-Elmer Model 257 spectrophotometer. NMR spectra were recorded on a Varian Model A-60 instrument with $(Me)_4Si$ as internal standard and $CDCl_3$ as solvent. The IR and NMR spectra of compounds **1–6** were consistent with the assigned structures. Thin-layer chromatography aided in the determination of compound purity. Visualization reagents used were 10% phosphomolybdic acid in EtOH and 0.3% ninhydrin in $n$-BuOH–HOAc.

**2-(3,4-Dimethoxybenzylidine)cyclopentanone (1).** Veratraldehyde (20 g, 120 mmol) and 4-(1-cyclopentenyl)morpholine (22.0 g, 144 mmol) in 100 mL of benzene containing 200–300 mg of $p$-toluenesulfonic acid were heated at reflux with azeotropic removal of water for 6 h. After the mixture was cooled, 36 mL of 6 N HCl was added dropwise with stirring over 15 min. Stirring was continued 20 min longer, and the benzene phase was separated, washed with three portions of saturated NaCl, and dried over $Na_2SO_4$. The solvent was removed in vacuo. The residue was crystallized from EtOAc to yield 15.3 g (55%) of yellow crystals: mp 116–117 °C (lit.[13] mp 113–114 °C). An additional 5.8 g (21%) of product, mp 115–116 °C, was recovered from the acidic aqueous fraction. Anal. ($C_{14}H_{16}O_3$) C, H.

**2-(3,4-Dimethoxybenzylidine)cyclopentanone *O*-Methyloxime (2).** Compound **1** (63.6 g, 270 mmol) and methoxyamine hydrochloride (27.6 g, 330 mmol) were refluxed in 1 L of pyridine for 19.5 h. After cooling, the reaction mixture was poured into 3 L of a stirred ice–water slurry and allowed to stand for 2 h. The solids were filtered, washed with 1.5 L of water and 250 mL of petroleum ether (30 °C), air-dried, and crystallized from MeOH to yield 57.8 g (82%) of tan crystals, mp 113.5–116 °C. Anal. ($C_{15}H_{19}NO_3$) C, H, N.

***cis*-2-(3,4-Dimethoxybenzyl)cyclopentylamine Hydrochloride (3).** Compound **2** (56.8 g, 217 mmol) was dissolved in 1 L of methylcellosolve, and 22.7 g of washed Raney nickel catalyst (W.R. Grace, grade 28) was added. The mixture was hydrogenated at 45 psi for 11 h. The solution was filtered and concentrated in vacuo. The crude, syrupy product was air-dried in an evaporating dish with periodic additions of 1,2-dimethoxyethane and EtOAc until a gray amorphous solid was obtained. The hydrochloride salt was prepared by dissolving the crude base in EtOAc–MeOH and treating with ethereal HCl. Filtration and two crystallizations from EtOAc–MeOH gave 33.5 g (66%) of fine white needles, mp 150–153 °C; TLC $R_f$ 0.39 (silica gel G; $Et_2NH$–EtOAc, 1:20). Anal. ($C_{14}H_{22}NO_2Cl$) C, H, N, Cl.

***trans*-2-(3,4-Dimethoxybenzyl)cyclopentylamine Hydrochloride (4).** Over 4.5 h, a solution of **2** (56.4 g, 216 mmol) in 800 mL of dry THF was added dropwise with stirring, under nitrogen, to 1 M $BH_3$/THF (1.3 L, 1.3 mol) in a 3-L, three-necked flask equipped with a magnetic stirrer, reflux condenser, and gas inlet and outlet tubes. The mixture was refluxed for 2.5 h and stirred at ambient temperature overnight. The borane adduct intermediate was isolated after cooling (ice bath) and adding 200 mL of water, dropwise with stirring. The temperature was maintained at 7–10 °C for 3.5 h. The solvent was removed in vacuo to give a white semisolid organoborane. This was hydrolyzed to the free base by refluxing for 4 h in 425 mL of 20% aqueous KOH containing 10 mL of MeOH. The clear solution was cooled to room temperature and extracted three times with 500-mL portions of $CH_2Cl_2$. The organic extracts were combined, washed with four portions of saturated NaCl, dried over mixed $Na_2SO_4$–$MgSO_4$, and concentrated in vacuo to a yellow oil. The oil was dissolved in 50 mL of EtOH–EtOAc–acetone (1:1:1) and treated with gaseous HCl. The acidic solution was diluted to 125 mL with dry acetone, refrigerated for 2 days, and filtered to yield 10.1 g (17%) of white crystalline product, mp 196–198 °C (anal. sample from EtOAc–MeOH, mp 201–202 °C); TLC $R_f$ 0.46 (silica

(23) G. Stork, A. Brizzolara, H. Landesman, J. Szmuskovicz, and R. Terrell, *J. Am. Chem. Soc.*, **85**, 207 (1963).

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

David C. Remy,*† Susan F. Britcher,† Paul S. Anderson,† Patrice C. Bélanger,‡ Yves Girard,‡ and B. V. Clineschmidt†,§

*Merck Sharp & Dohme Research Laboratories and Merck Institute for Therapeutic Research, West Point, Pennsylvania 19486, and Merck Frosst Laboratories, Pointe Claire/Dorval, Quebec, Canada H9R 4P8.*
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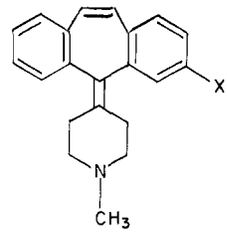
The synthesis and orexigenic activity of some unsubstituted and *Bz*-carboxylic acid substituted 1-methyl-4-piperidylidenepyrrolo[2,1-*b*][3]benzazepine and dibenzocycloheptene derivatives are described. 10,11-Dihydro-3-carboxycyproheptadine (**7c**) has been selected for clinical evaluation as an orexigenic 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

† Merck Sharp & Dohme Research Laboratories.
‡ Merck Frosst Laboratories.
§ Merck Institute for Therapeutic Research.

(1) J. W. Saleh, M. U. Yang, S. A. Hashim, and T. B. Itallie, *Clin. Res.*, **24**(3), 503A (1976).
(2) G. J. Pawloski, *Curr. Ther. Res.*, 18(5), 673 (1975).
(3) P. Zanetti and G. Castelli, *Clin. Ter. (Rome)*, **66**(4), 375 (1973).
(4) A. K. Farra, *Praxis*, **62**, 798 (1973).
(5) J. Inouye and F. Ishihara, *Shinryo Shinyaku*, **10**(5), 1089 (1973).
(6) S. C. Goldberg, R. C. Casper, and E. D. Eckert, *Psychopharmacol. Bull.*, **16**(2), 29 (1980).
(7) K. A. Halmi and S. C. Goldberg, *Psychopharmacol. Bull.*, **14**(2), 31 (1978).
(8) S. C. Goldberg, K. A. Halmi, E. D. Eckert, R. C. Casper, and J. M. Davis, *Br. J. Psychiatry*, **134**, 67 (1979).
(9) W. Molleney, *Z. Allgemeinmed. Landarzt*, **48**(12), 607 (1972).

0022-2623/82/1825-0231$01.25/0 