trans analogue lie on almost the same plane, while the cyclohexane ring in the cis analogue projects to the direction of the z axis (chelate ring, x–y plane). The steric effect to the direction of the z axis is distinctly different in the complexation of nickel ion with dach isomers,[14,15] and the steric difference allowed separation of two geometrical isomers from the dach mixture.[16] Steric character of the platinum complexes derived from *cis*- and *trans*-dach is different in the planarity and rigidity between the cyclohexane and chelate rings. This difference may affect the fitting of the platinum complexes to DNA and may lead to a significant difference in their antitumor activity. The binding of these platinum complexes to calf-thymus DNA causes destabilization of the double helix by local denaturation, and the degree of destabilization due to the trans analogue is more than that of the cis analogue, though small.[17] At any rate, it is very interesting that the conformational difference on nonleaving group results in different response against the tumor system tested. Among the platinum complexes tested in this work, Pt(oxalato)(*cis*-dach) seems to be a promising agent because of its high activity and its good solubility.

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2,5-Bis(3,4-dimethoxybenzyl)cyclopentylamine, a Peripheral Dopamine Blocking Agent

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2,5-Bis(3,4-dimethoxybenzyl)cyclopentylamine hydrochloride has been synthesized. The intermediate 2,5-bis-(3,4-dimethoxybenzyl)cyclopentanone was formed in 91.8% yield using a sodium methoxide catalyzed aldol condensation and catalytic reduction. The oxime of this ketone was catalytically hydrogenated to the amine which was converted to the hydrochloride (76%). The amine hydrochloride was found to be an effective antagonist to the low-dose hypotensive effect of dopamine; the half-life of this effect was 18 min. At dopamine doses of 3 mg/kg in the atropinized and phenoxybenzamine treated dog, the ED_{50} for blockade was 4–5 μmol/kg. In direct contrast to its peripheral dopamine blocking activity, the compound potentiates apomorphine-induced stereotypy.

In contrast to dopaminergic agonists,[1-3] antidopaminergic compounds show great structural variety[4] and, in a few cases, display selectivity for specific dopamine receptor systems. It is on the basis of ergometrine and haloperidol selectivity that the concept of dopamine excitatory and dopamine inhibitory brain receptors evolved.[3] Similarly, the central dopamine blocking action and lack of peripheral dopamine blocking activity by pimozide[5] reveal considerable differences in the chemistry of dopamine-specific receptors. We have been interested in dopamine-receptor chemical topography[6] and now report on a new peripheral dopamine blocking agent. This compound, 2,5-bis(3,4-dimethoxybenzyl)cyclopentylamine (**4**), in contrast to its peripheral dopamine blocking action, potentiates apomorphine-induced mouse stereotypy,[7] a measure of striatal dopaminergic stimulation, and rapidly depletes brain norepinephrine.[8]

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Experimental Section

Synthesis. Cyclopentanone and veratraldehyde were purchased from the Aldrich Chemical Co., Milwaukee, Wis., and used without further purification. Melting points were determined using a Fisher-Johns apparatus and are corrected. Elemental analyses were performed by the Analytical Research Department of Abbott Laboratories. Where analyses are indicated only by symbols of the elements, the results were within ±0.4% of theory. IR spectra were determined using a Perkin-Elmer Model 257 spectrometer and KCl pellets. NMR spectra were determined with a Varian Model A-60A instrument using $(Me)_4Si$ as an internal standard and Me_2SO-d_6 as solvent. The IR and NMR spectra of intermediates **1**–**3** and final product **4** were consistent with the assigned structures. Thin-layer chromatography as well as NMR integration was used to establish that each was a single compound.

2,5-Bis(3,4-dimethoxybenzyl)cyclopentanone (1). Cyclopentanone (16.8 g, 0.20 mol) and veratraldehyde (66.4 g, 0.40 mol) were dissolved in MeOH (250 cm[3]) containing 4 g of Na. The

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mixture was stirred without heating and crystalline reaction product precipitated overnight. The product was collected on a filter, washed to neutrality with distilled water, and dried on the filter mat to yield 61 g (80%) of bright yellow needles, mp 190–191 °C (lit.[9] mp 193–194 °C).

2,5-Bis(3,4-dimethoxybenzyl)cyclopentanone (2). Compound 1 (9.5 g, 0.025 mol) was dissolved in 250 ml of DMF and hydrogenated at 3 atm of H_2 pressure using 1.2 g of Raney nickel (W. R. Grace, grade 28); uptake was complete in 45 min (pressure drop measurement). The solution was filtered to remove catalyst and concentrated to dryness with a rotary evaporator. The yield of pale yellow plates (crystallized from MeOH) was 8.8 g (91.8%), mp 94–96 °C. Anal. ($C_{23}H_{28}O_5$) C, H.

2,5-Bis(3,4-dimethoxybenzyl)cyclopentanone Oxime (3). Compound 2 (8.8 g, 0.023 mol) was dissolved in 100 mL of EtOH (absolute) and 100 mL of pyridine containing 8.8 g (0.13 mol) of hydroxylamine hydrochloride and heated on a steam bath overnight. The mixture was concentrated to an oil using a rotary evaporator. The residue was diluted with water and cooled in ice. The crude product (gum) was washed free of pyridine and hydroxylamine with distilled water by decanting; it was dried by azeotroping with EtOH. Anal. ($C_{23}H_{29}NO_5$) C, H, N.

2,5-Bis(3,4-dimethoxybenzyl)cyclopentylamine Hydrochloride (4). Compound 3 (10 g, 0.025 mol) was dissolved in 100 mL of MeOH containing 5 mL of liquid NH_3 and hydrogenated at 3 atm of H_2 pressure using 2.0 g of Raney nickel (W. R. Grace, grade 28); uptake was complete in 12 h (pressure drop measurement). The solution was filtered to remove catalyst and concentrated with a rotary evaporator. The residue was taken up in ether, filtered to remove insoluble matter, and concentrated at room temperature to an oil with a rotary evaporator. The oil was dissolved in ether and treated with HCl–MeOH to obtain hydrochloride which was collected on a filter and crystallized from acetone to yield 7.8 g (76%) of white feathery needles, mp 119.5–122 °C. Anal. ($C_{23}H_{32}NO_4Cl$) C, H, N.

Cardiovascular Experiments. A population comprising 30 mongrel dogs of both sexes and in the weight range of 6.75–13.0 kg was used. Sodium pentobarbital anesthesia, 20 mg/kg iv, was used with morphine sulfate, 5 mg/kg, premedication. Following endotracheal intubation, the right femoral artery and vein were cannulated with polyethylene tubing. All subsequent injections were made via the indwelling venous catheter followed by 2 mL of heparinized saline (0.9%) flush. Blood pressure and heart rate measurements were made via the arterial catheter using a Model 4 Physiograph instrument equipped with a P-1000 A transducer. The animals were atropinized, 1 mg/kg, to eliminate reflex vagal bradycardia and tested for autonomic responsiveness with norepinephrine, 0.1–0.2 μg/kg, and *N*-isopropylnorepinephrine, 0.1–0.2 μg/kg. Adequacy of atropine blockade was indicated by a lack of bradycardia during norepinephrine-induced pressor responses. Sensitivity to dopamine was tested with two doses in the depressor dose range, 1–5 μg/kg, and one dose in the pressor dose range, 10 μg/kg and above. Other drugs used to explore mechanistic aspects of 4 were phentolamine, 1 mg/kg, and propranolol, 1 mg/kg. In selected experiments, the pressor action of dopamine was eliminated with phenoxybenzamine, 5 mg/kg. All drugs were administered in 2 mL of saline (0.9%).

Mouse Stereotypy Experiments. Male Swiss–Webster mice (20–30 g), housed in a light- and temperature-controlled environment and fed ad libitum, were used in the study. All injections were ip in 0.9% saline and in a volume no greater than 0.2 mL. Animals were dosed with either 0.9% saline (control), 0.1 mg/kg of haloperidol, or various loadings of compound 4. Thirty minutes later, all animals were injected with 1 mg/kg of apomorphine hydrochloride sc in saline as above. They were placed in individual cylindrical wire mesh cages (22.5 × 22.5 cm). After about 5 min of exploratory activity, control-treated animals tended to adopt vertical positions, either holding the cage walls with the forefeet or climbing the wall to maintain a vertical position. In contrast, after a similar period of exploratory activity, the haloperidol-pretreated animals tended to remain on the floor of the cage, i.e., they demonstrated a lack of sterotypy.

The sterotypic climbing was scored as follows: all paws on the cage floor = 0, forefeet on the wall = 1, clinging to the wall with all paws = 2. Two observations were made on each mouse, 10 and 20 min after dosing with apomorphine hydrochloride. The two scores for each animal were averaged. Ten animals were used for each result expressed in Table I. For each dose of compound 4 used in the apomorphine experiments, a similar control population was studied to assess behavioral effects of the drug.

Table I. Effect of 4 on Apomorphine-Induced Mouse Climbing

	dose, mg/kg[a]	av climbing score ± SE
saline		1.35 ± 0.11
acute haloperidol	0.1	0.50 ± 0.14[b]
acute 4	2.5 (5.94)	1.35 ± 0.25
	5.0 (11.9)	1.50 ± 0.21
	10.0 (23.8)	1.55 ± 0.17
	20.0 (47.5)	1.63 ± 0.16[c]
	25.0 (59.4)	1.67 ± 0.14[d]
	50.0 (119)	1.45 ± 0.23
	75.0 (178)	1.40 ± 0.22
	100.0 (237)	0.65 ± 0.22[b]
chronic 4	2.5 (5.94)	1.80 ± 0.13[b]
	5.0 (11.9)	1.65 ± 0.15[c]
	10.0 (23.8)	1.60 ± 0.16
	25.0 (59.4)	1.55 ± 0.17

[a] Each experimental group comprised 10 animals. All subjects received 1 mg/kg of apomorphine hydrochloride sc 30 min after haloperidol, compound 4, or saline. Parenthesized numbers indicate dosages in μmol/kg. [b] $p < 0.002$ significantly different from saline + apomorphine by the two-tailed Student's *t* test. [c] $p < 0.02$. [d] $p < 0.05$.

Results and Discussion

Cyclopentanone and veratraldehyde were subjected to aldol condensation using internally generated sodium methoxide as catalyst. The resulting bis condensation product 1 was obtained in 80% yield and catalytically hydrogenated with no prior crystallization. The hydrogenation product 2 was converted to oxime 3 using pyridine catalyst. The crude product was thoroughly washed to remove pyridine residues in order to avoid poisoning the catalyst used in reduction of 2. The desired amine 4 was obtained as an oil on catalytic hydrogenation of the oxime; it was converted to the hydrochloride and purified by crystallization from acetone. The stereochemistry of the amine cannot be ascertained from either the IR or ^1H NMR spectrum. However, in view of the reasonably well understood mechanism of oxime reduction in basic media,[10] we are inclined to a structure with the amine function trans to the 3,4-dimethoxybenzyl groups, which in turn are cis to one another.

The acute effect of 4 in the pentobarbital anesthesized, morphine premedicated and atropinized dog is a transient vasodepression. This action is manifest as a dose-related drop in systolic and diastolic pressure. The threshold dose for this effect, 1.2–1.4 μmol/kg, was determined from the linear plot of percent decrease in mean blood pressure against log dose. At a dose of 2.4 μmol/kg, the decrease is an average of 10% and the duration of effect less than 1 min. At doses from 95 to 120 μmol/kg, the acute cardiovascular effect is lethal. The cardiovascular action is not blocked by haloperidol, metoclopramide, or propranolol and, in our view, is a direct effect on the heart musculature rather than any dopaminergic or autonomic effect. In doses up to 71 μmol/kg, the compound shows no antagonism to the chronotropic, inotropic, or blood pressure effects of norepinephrine or *N*-isopropylnorepinephrine.

It has been reported that doses of dopamine in the 1–9 μg/kg range yield a lowering of the dogs' mean systolic and diastolic blood pressure by virtue of action at dopamine selective and sensitive receptors.[5] At about 3 μg/kg, the lowering of blood pressure is maximum and higher doses

will show an additional pressor effect due to action at α-adrenergic receptors. The dopamine dose used in this work was 3 μg/kg; in dopamine responsive dogs, this dose produces a mean blood pressure drop of from 17 to 21%. In every case, 3 μg/kg produced a transient pressor effect before the longer and quantitatively greater depressor action supervened. When **4** was deployed against dopamine given at 3 μg/kg, a dose-related reduction in the depressor response occurred. The threshold dose for this antagonism was from 0.7 to 1.2 μmol/kg. Reduction of the dopamine depressor effect was accompanied by enhancement of the pressor phase of its action. In the presence of this transitory elevation in blood pressure, it was particularly difficult to determine when blockade was complete. As expected, the pressor action was eliminated by predosing with phenoxybenzamine. Dose–response studies of dopamine blockade by **4** were made in the α-adrenergic blocker treated animals. In this population, even though subject to much interanimal variability, complete blockade of the dopamine depressor action occurred at doses of **4** ranging from 12 to 17 μmol/kg. As determined from a linear plot of log dose vs. percent antagonism of dopamine depressor effect, the ED_{50} varied from 4 to 5 μmol/kg. The time course of **4** action was studied in one animal dosed with 6 μ/kg of the compound. The residual blockade was determined at 5-min intervals with 5 μg/kg of dopamine challenge. Using the linear plot of log residual blockade against time, the half-life of drug action was determined to be 18 min.

Apomorphine-induced climbing stereotypy was antagonized by pretreatment with 0.1 mg/kg of haloperidol (Table I). In contrast, compound **4** potentiated climbing behavior, the trend reaching statistical significance at 42.5 and 59.4 μmol/kg. The climbing inhibition obtained with 237 μmol/kg of **4** is evidence of the toxicity seen with this dose rather than a specific antagonism.[8] Chronic administration (7 days) of **4** yielded greater climbing potentiation, the maximal effect following 5.6 μmol/kg dosage.

This measure of stereotypy, as previously employed in this laboratory,[11] is a reliable method of assessing mouse striatal dopaminergic stimulation.[12] The failure of **4** to attenuate the climbing behavior indicates a lack of striatal dopamine blocking activity in contrast to the antidopamine properties of **4** seen peripherally. Thus, **4** is one of a few dopamine antagonists which provides evidence for the existence of multiple dopamine receptors.

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Synthesis and Antinociceptive Activity of 7-Methoxycodeine

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(−)-7-Methoxycodeine was synthesized from (−)-1-bromosinomeninone in three steps with an overall yield of 29%. The introduction of the 7-methoxy group into the C ring of codeine did not decrease its oral activity. 7-Methoxycodeine was unstable in acidic media. Its oral activity was, however, not likely to be due to conversion to the acid-stable (−)-sinomeninone, since the latter was orally inactive.

During model studies pertaining to our syntheses of (+)-morphine, (+)-codeine, (+)-heroin, and (+)-naloxone,[1,2] we prepared (−)-1-bromosinomeninone (**1**) both as a possible precursor of (−)-codeine and as the starting material for (−)-7-methoxycodeine (**6**). Since a vinylic methoxy group in the C ring of the opioids represents an uncommon substitution pattern, and was accessible by these methods, we decided to examine the antinociceptive activity of the compound.

The aromatic methoxy group in codeine reduces overall antinociceptive activity, when compared with the effect of the phenolic hydroxyl of morphine. However, the ratio of parenteral to oral activity is greater in codeine than in morphine (see Table I), possibly because the more hydrophobic molecule can more easily reach the opiate receptors in the brain and because of a decreased rate of metabolic removal due to the blocked phenolic hydroxyl group. It has been noted that the relatively high in vivo potency of codeine, when compared with its remarkably low binding affinity to the opiate receptors in rat-brain homogenate assays,[3] could be caused by a metabolic conversion to morphine in situ.[4-7] We were, then, interested in seeing whether a vinylic methoxy group would further effect the antinociceptive activity of codeine.

Synthesis. Enol methylation of the known (−)-1-bromosinomeninone (**1**)[8] gave a 1:1 mixture of (+)-1-bromosinomenine (**2**) and (−)-1-bromoisosinomenine (**3**) (Scheme I). Compound **2** was essentially identical, except

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