cording to the procedure for **14** from 16 g (0.067 mol) of **13**, affording 13.8 g (93.6%) of a colorless liquid: bp 110–115 °C (0.03 mm); NMR ($CDCl_3$) δ 0.7–1.7 [m, 7, $(CH_2)_2CH_3$], 3.84 (s, 3, CH_3O), 3.87 (s, 3, CH_3O), 6.7–7.0 (m, 3, aromatic), with calculated ABX_2 for $CH{=}CHCH_2$ exhibiting δ_A 6.37, δ_B 6.02, δ_X 2.19 (d of t; deceptively simple q) with J_{AB} = 16.0 Hz, J_{AX} = 0.0 Hz, J_{BX} = 6.0 Hz. Anal. ($C_{14}H_{20}O_2$) C, H.

2-Methyl-3-(dimethylamino)-5,6-dimethoxy-1-indene hydrochloride (5) was prepared according to the method of Witiak et al.[2] for the preparation of methylenedioxy analogues **1–4** from 1-(3,4-dimethoxyphenyl)-1-propene (**14**; 9.0 g, 0.05 mol). The resulting dark mixture was not distilled[2] but dissolved in anhydrous Et_2O and acidified with gaseous HCl. The solid was filtered and recrystallized (Et_2O–EtOH), affording 6.2 g (45.1%) of white crystals: mp 156–157 °C; NMR δ ($CDCl_3$) 2.31 (s, 3, CH_3), 2.71 (d, 3, NCH_3, J = 5 Hz), 2.88 (d, 3, NCH_3, J = 5 Hz), 3.73 (s, 3, CH_3O), 3.76 (s, 3, CH_3O), 4.63 (s, 1, H_3), 6.61 (s, 1, H_1), 6.79 (s, 1, H_7), 7.82 (s, 1, H_4). Anal. ($C_{14}H_{20}O_2NCl{\cdot}0.5H_2O$) C, H, N.

2-Ethyl-3-(dimethylamino)-5,6-dimethoxy-1-indene hydrochloride (6) was prepared according to the procedure for **5** from **15** (10.0 g, 0.052 mol), affording 13.2 g (62.3%) of white crystals: mp 161–162 °C; NMR δ ($CDCl_3$) 1.28 (t, 3, CH_3, J = 7 Hz), 2.4–2.8 (m, 2, CH_2CH_3), 2.65 [s, 6, $(CH_3)_2N$], 3.90 (s, 3, CH_3O), 3.93 (s, 3, CH_3O), 4.71 (s, 1, H_3), 6.62 (s, 1, H_1), 6.81 (s, 1, H_7), 7.73 (s, 1, H_4). Anal. ($C_{15}H_{22}O_2NCl{\cdot}H_2O$) C, H, N.

2-Propyl-3-(dimethylamino)-5,6-dimethoxy-1-indene hydrochloride (7) was prepared according to the procedure for **5** from **16** (14.0 g, 0.068 mol), affording 13.4 g (66.2%) of white crystals: mp 153–154.5 °C; NMR δ ($CDCl_3$) 1.03 (t, 3, CH_2CH_3, J = 6.5 Hz), 1.4–2.0 (m, 2, $CH_2CH_2CH_3$), 2.4–3.0 [m, 8, $(CH_3)_2N$, $CH_2CH_2CH_3$], 3.91 (s, 3, CH_3O), 3.98 (s, 3, CH_3O), 4.65 (s, 1, H_3), 6.66 (s, 1, H_1), 6.83 (s, 1, H_7), 7.84 (s, 1, H_4). Anal. ($C_{16}H_{24}O_2NCl$) C, H, N, Cl.

2-Butyl-3-(dimethylamino)-5,6-dimethoxy-1-indene hydrochloride (8) was prepared according to the procedure for **5** from **17** (15.0 g, 0.068 mol), affording 13.2 g (62.3%) of white crystals: mp 157–158 °C; NMR δ ($CDCl_3$) 0.96 (t, 3, CH_2CH_3, J = 6.5 Hz), 1.2–1.9 [m, 4, $(CH_2)_2CH_3$], 2.4–2.9 [m, 8, $(CH_3)_2N$, $CH_2(CH_2)_3CH_3$], 3.90 (s, 3, CH_3O), 3.93 (s, 3, CH_3O), 4.62 (s, 1, H_3), 6.62 (s, 1, H_1), 6.80 (s, 1, H_7), 7.82 (s, 1, H_4). Anal. ($C_{17}H_{26}O_2NCl$) C, H, N, Cl.

Pharmacology. Methods employed were similar to those described previously by Rahwan et al.[3] Briefly, female albino rats (200–250 g) were sacrificed by cervical dislocation and sections of the ileum were prepared for isotonic contraction recordings under 500 mg of tension in 10-mL tissue baths containing a bathing solution (37 °C) having the following composition (g/L): NaCl (8.086); KCl (0.20); $CaCl_2{\cdot}2H_2O$ (0.52); $MgCl_2{\cdot}2H_2O$ (0.42); $NaH_2PO_4{\cdot}H_2O$ (0.10); $NaHCO_3$ (1.0); dextrose (1.0). Recordings were made with an isotonic MK II myograph transducer and a Physiograph 4 recorder (E & M Instrument Co., Houston, TX). The bathing solution was aerated with 5% CO_2 in O_2. A 30-min equilibration time was allowed prior to all experiments.

In each experiment a control response to $PGF_{2\alpha}$ (3×10^{-7} M bath concentration) or acetylcholine (AcCh; 10^{-6} M bath concentration) was obtained, and the bath was then washed three times prior to incubation of the tissue with any of the test compounds, **5–8**. The test compound was added to the bath and left in contact with the ileum for 3 min. $PGF_{2\alpha}$ (3×10^{-7} M) or AcCh (10^{-6} M) was then added to the bath and the contractions were recorded. After 5 min the bath was washed three times and the control response to $PGF_{2\alpha}$ or AcCh regained. All values were calculated as percent of the control responses to $PGF_{2\alpha}$ or AcCh. A separate ileum strip was used for each compound and each concentration. The tissues did not demonstrate any potentiation or tachyphylaxis upon repeated exposure to $PGF_{2\alpha}$ or AcCh alone.

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(1) Support of this work by U.S. Public Health Service Grant HL-21670 from the National Heart, Lung and Blood Institute is gratefully acknowledged.
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Antitumor Activity of 1,2-Diaminocyclohexane–Platinum Complexes against Sarcoma-180 Ascites Form

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Received May 1, 1978

Platinum complexes derived from three isomers of 1,2-diaminocyclohexane have been synthesized and their antitumor activities were evaluated against ascites Sarcoma-180. All the platinum complexes had high antitumor activity. Platinum complexes derived from *cis*-1,2-diaminocyclohexane were more effective than those derived from *trans-l*- and *trans-d*-1,2-diaminocyclohexane. Among the platinum complexes tested, oxalato(*cis*-1,2-diaminocyclohexane)platinum had a remarkably high therapeutic index. Modification of the nonleaving group as well as that of the leaving group is important in order to find better antitumor platinum complexes.

Since the discovery of antitumor activity of (*cis*-dichlorodiammine)platinum,[1] a great number of new platinum complexes were synthesized and tested. Among them, (dichloro-1,2-diaminocyclohexane)platinum, which was synthesized and tested by Connors et al.,[2] Cleare and Hoeschele,[3] Gale et al.,[4] and Speer et al.,[5] had a high antitumor activity against various tumor systems. Unfortunately, its therapeutic index was disappointingly low. Modification of the leaving group was attempted to find better complexes having higher values of therapeutic indices, and malonato- and sulfato(1,2-diaminocyclohexane)platinum[6-9] were consequently prepared. Both the

0022-2623/78/1821-1315$01.00/0

Table I. Analytical and Infrared Data of Platinum Complexes

compd	formula (analyses)	infrared data, cm^{-1}
$PtCl_2$(*cis*-dach)	$C_6H_{14}N_2Cl_2Pt$ (C, H, N)	ν_{NH_2} 3245 s, 3193 s, 3118 m; δ_{NH_2} 1569 s; ρ_{NH_2} 763 m, 739 m
$PtCl_2$(*trans-l*-dach)	$C_6H_{14}N_2Cl_2Pt$ (C, H, N)	ν_{NH_2} 3267 s, 3185 s, 3104 m; δ_{NH_2} 1564 s; ρ_{NH_2} 756 s
$PtCl_2$(*trans-d*-dach)	$C_6H_{14}N_2Cl_2Pt$ (C, H, N)	
Pt(oxalato)(*cis*-dach)	$C_8H_{14}N_2O_4Pt$ (C, H, N)	ν_{NH_2} 3176 s, 3104 s; δ_{NH_2} 1613 m; $\nu_{C=O}$ 1708 s, 1693 s, 1667 s; ν_{C-O} 1392 s
Pt(oxalato)(*trans-l*-dach)	$C_8H_{14}N_2O_4Pt$ (C, H, N)	ν_{NH_2} 3206 s, 3156 s, 3088 s; δ_{NH_2} 1608 m; $\nu_{C=O}$ 1697 s, 1670 s, 1659 s; ν_{C-O} 1397 s
Pt(oxalato)(*trans-d*-dach)	$C_8H_{14}N_2O_4Pt$ (C, H, N)	
Pt(malonato)(*cis*-dach)	$C_9H_{16}N_2O_4Pt$ (C, H, N)	ν_{NH_2} 3192 s, 3167 s; δ_{NH_2} 1590 sh; $\nu_{C=O}$ 1663 s, 1628 s; ν_{C-O} 1380 s
Pt(malonato)(*trans-l*-dach)	$C_9H_{16}N_2O_4Pt$ (C, H, N)	ν_{NH_2} 3173 s, 3096 s; δ_{NH_2} 1565 m; $\nu_{C=O}$ 1660 s, 1621 s; ν_{C-O} 1408 s
Pt(malonato)(*trans-d*-dach)	$C_9H_{16}N_2O_4Pt$ (C, H, N)	

complexes were reported to exhibit not only high therapeutic indices but also excellent synergism when administered in combination with cyclophosphamide. However, no attention has been paid to the isomers of 1,2-diaminocyclohexane (abbreviation, dach), *cis*-, *trans-l*- and *trans-d*-dach.

In the present work, we examined how antitumor activity of platinum complexes of the three isomers varies with conformation of their nonleaving group using Sarcoma-180 ascites in ddN mice.

Experimental Section

Dichloro complexes, $PtCl_2$(*cis*-dach), $PtCl_2$(*trans-l*-dach), and $PtCl_2$(*trans-d*-dach), were prepared by mixing equivalent moles of K_2PtCl_4 with each isomer of dach in aqueous solution. Pt(oxalato)(*cis*-dach) was prepared by the following method. $PtCl_2$(*cis*-dach) (2 mmol) was dissolved in about 100 mL of water by heating, and this solution was added immediately to 5 mL of $AgNO_3$ (4 mmol) solution. The mixture was stirred for at least 5 h at room temperature in the dark. The AgCl that precipitated out was removed by filtration, the clear filtrate was evaporated to about 10 mL, and then the solution was added to about 5 mL of aqueous solution containing potassium oxalate (2 mmol). The solution was allowed to stand for 24 h at room temperature and then evaporated to dryness. Recrystallization of the residual solid from water gave colorless crystals of Pt(oxalato)(*cis*-dach).

Other complexes, Pt(malonato)(*cis*-dach), Pt(malonato)(*trans-l*-dach), and Pt(malonato)(*trans-d*-dach), were prepared by a similar procedure. Table I shows analytical and infrared data of these complexes. As expected, the infrared spectrum for the complex of the *trans-l* analogue quite agreed with that of the *trans-d* analogue.

Antitumor Activity. A group of six female ddN mice weighing 20 ± 2 g were implanted intraperitoneally (ip) with 1×10^7 cells of Sarcoma-180. All platinum complexes to be tested were suspended in 0.5% carboxymethylcellulose in 0.9% NaCl solution and injected ip at various doses once daily for 5 days, starting 24 h after transplantation. Antitumor activity was evaluated by the total packed cell volume (TPCV) ratio (T/C, %) on the seventh day after transplantation.[12] Toxicity was evaluated with LD_{10} on the evaluation day (seventh day). The therapeutic index (LD_{10}/ED_{90}) was also calculated.

Solubility of the Complexes. An appropriate amount of the complex was added to about 2 mL of water. After being shaken for 3 days at 37 °C, the solution was filtered and the filtrate was diluted to a suitable volume. To 1.0 mL of this solution, 1.0 mL of 0.5 N HCl solution containing 40 000 ppm of $LaCl_3$ was added. The platinum content in this solution was determined by use of an atomic absorption spectrophotometer. Solubility was calculated from the platinum content.

Results and Discussion

The antitumor activities of the platinum complexes prepared from each isomer of dach were evaluated against the ascites form of Sarcoma-180 by ip administration. Cleare and Hoeschele[3] reported on the antitumor activities of $PtCl_2$(dach) and Pt(malonato)(dach) against Sarcoma-180. Neither of the complexes appeared especially active against Sarcoma-180. On the other hand, both the complexes were quite active against leukemia L1210.[4-7] In the present work, all the complexes tested showed a high antitumor activity against Sarcoma-180 ascites as indicated in Table II.

When antitumor activities of the platinum complexes of three isomers of dach are compared with each other, it appears that the cis analogues are somewhat more efficacious than the corresponding trans analogues (Table III). Among the three dichloro complexes, the toxicity of the cis analogue is lower than that of trans analogue, and the therapeutic index of the former is better than that of the latter. The two trans analogues have almost the same efficacy. We indicated in a previous communication[10] that they were quite active against leukemia L1210 and P-388 in BDF_1 mice, and the order of the percentage increase in life span (ILS, %) of the three dichloro complexes decreased in the following order: for L1210, $PtCl_2$(*trans-l*-dach) (279%) > $PtCl_2$(*trans-d*-dach) (236%) > $PtCl_2$(*cis*-dach) (140%); for P-388, $PtCl_2$(*trans-l*-dach) (128%) = $PtCl_2$(*trans-d*-dach) (128%) > $PtCl_2$(*cis*-dach) (106%). Both trans analogues were more efficacious than the corresponding cis analogue against L1210 and P-388. This is similar to the order of the potency against Sarcoma-180 as compared with ED_{90}. However, the therapeutic index of the cis analogue against Sarcoma-180 ascites is better than that of the corresponding trans analogues.

The most fascinating platinum complex found in this work is Pt(oxalato)(*cis*-dach). In the study on modification of the leaving group in antitumor active ethylenediamine (abbreviation, en) platinum complexes,[11] Pt(malonato)(en) showed higher activity than $PtCl_2$(en). However, Pt(oxalato)(en) had extremely high neuromuscular toxicity. In the case of platinum complexes derived from each isomer of dach, substitution of the dichloro leaving group with the oxalato group led to the appearance of an extremely high antitumor activity. The oxalato complexes were administered for five consecutive days, and they seem to have little neuromuscular toxicity. The activity of Pt(oxalato)(*cis*-dach) is better than that of the corresponding trans analogues in potency (ED_{90} = 0.72) and therapeutic index (14–42). It is noteworthy that Pt(oxalato)(*cis*-dach) has a remarkably high antitumor activity, comparable to that of 5-fluorouracil, against Sarcoma-180 ascites.[12]

There is little difference in the activities of Pt(malanato)(*cis*-dach) and Pt(malonato)(*trans-l*-dach) and Pt(malonato)(*trans-d*-dach). Appearance of the activity in the malonato complexes requires a larger dosage than that of the corresponding dichloro or oxalato complexes. However, therapeutic indices of the malonato complexes seemed to be larger relative to that of the dichloro complexes.

Table IV shows the solubility of these platinum complexes in water. This is very important from the thera-

Table II. Results of Antitumor Screening of Platinum Complexes of 1,2-Diaminocyclohexane Isomers in Sarcoma-180

compd	dose, (mg/kg)/day	tumor growth[a] (T/C, %)	body wt change[b] (T/C, g)	results[c]	mortality[d] (died/used)
Pt(*trans-d*-dach)	10			toxic	5/6
	3	1	−1.1/0.5	+++	0/6
	1	28	0.6/1.4	++	0/6
$PtCl_2$(*trans-l*-dach)	10			toxic	6/6
	3	2	−4.2/0.5	+++	0/6
	1	18	0.1/1.4	++	0/6
$PtCl_2$(*cis*-dach)	30			toxic	6/6
	10	0	−7.8/0.5	+++	0/6
	3	3	−1.7/0.4	+++	0/6
	1	57	−0.5/1.4	+	0/6
Pt(oxalato)(*trans-d*-dach)	10			toxic	5/6
	3	11	−1.0/0.5	++	0/6
Pt(oxalato)(*trans-l*-dach)	10			toxic	4/6
	3	9	−1.4/0.5	+++	0/6
Pt(oxalato)(*cis*-dach)	30			toxic	6/6
	10	0	−3.1/0.6	+++	0/6
	3	0	−0.3/0.5	+++	0/6
	1	0	−1.1/0.4	+++	0/6
	0.5	20	−1.0/2.5	++	0/6
	0.3	83	−2.5/1.4	−	0/6
Pt(malonato)(*trans-d*-dach)	300			toxic	6/6
	100	0	−3.5/1.4	+++	0/6
	30	1	−1.4/0.6	+++	0/6
	10	47	0.2/0.5	+	0/6
Pt(malonato)(*trans-l*-dach)	300			toxic	6/6
	100	4	−4.9/1.4	+++	0/6
	30	1	−1.3/0.6	+++	0/6
	10	17	−1.1/0.5	++	0/6
	3	85	−1.7/1.4	−	0/6
Pt(malonato)(*cis*-dach)	300			toxic	6/6
	100	0	−1.4/1.4	+++	0/6
	30	0	0.2/0.6	+++	0/6
	10	61	0.9/0.5	+	0/6

[a] Total packed cell volume ratio for the ascites tumor. [b] Body weight gain (subtracted tumor weight) from the first day to the evaluating day (seventh day). [c] Antitumor activity was graded as − (100-66), + (65-41), ++ (40-11), and +++ (10-0) of T/C, %. [d] Number of dead animals/number of animals used.

Table III. Therapeutic Evaluation of Platinum Complexes of 1,2-Diaminocyclohexane Isomers

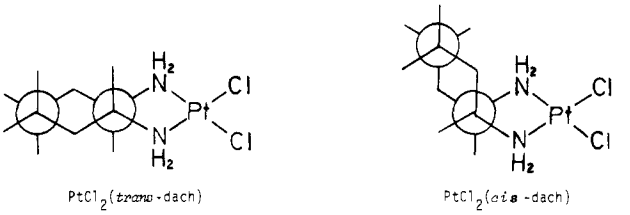
compd	ED_{90}, (mg/kg)/day	range of LD_{10}, (mg/kg)/day	range of therapeutic index[a]
$PtCl_2$(*trans-d*-dach)	1.6	3-10	2-6
$PtCl_2$(*trans-l*-dach)	1.4	3-10	2-7
$PtCl_2$(*cis*-dach)	2.2	10-30	5-14
Pt(oxalato)(*trans-d*-dach)	3.1	3-10	1-3
Pt(oxalato)(*trans-l*-dach)	2.8	3-10	1-4
Pt(oxalato)(*cis*-dach)	0.72	10-30	14-42
Pt(malonato)(*trans-d*-dach)	18	100-300	6-17
Pt(malonato)(*trans-l*-dach)	14	100-300	7-21
Pt(malonato)(*cis*-dach)	19	100-300	5-16

[a] Therapeutic index = LD_{10}/ED_{90}.

Table IV. Solubility of Platinum Complexes of 1,2-Diaminocyclohexane Isomers

compd	solubility, mg/mL
Pt(oxalato)(*cis*-dach)	5.6
Pt(oxalato)(*trans-l*-dach)	7.9
Pt(malonato)(*cis*-dach)	0.29
Pt(malonato)(*trans-l*-dach)	0.23
$PtCl_2$(*cis*-dach)	1.0
$PtCl_2$(*cis*-dach)	(0.67)[a]
$PtCl_2$(*trans-l*-dach)	0.26
$PtCl_2$(*trans-l*-dach)	(0.10)[a]

[a] Solubility in 1.0 M KCl solution at 37 °C.



$PtCl_2$(*trans*-dach) $PtCl_2$(*cis*-dach)

Figure 1. Newman projection of $PtCl_2$(*trans*-dach) and $PtCl_2$(*cis*-dach).

peutic point. Expectedly, the solubility of the complexes of *trans-l*-dach was essentially the same as that of *trans-d*-dach. For dichloro complexes, solubility of the cis analogue in water is about five times as much as that of the trans analogues. However, water solubility of these complexes depends mainly on the nature of the leaving group rather than on the conformation of dach. Pt(oxalato)(*cis*-dach) is considered to be the most promising platinum complex because of its high therapeutic index and its good solubility. Recently, Gale et al.[13] showed that $Pt(NO_3)_2$(dach) has a high antitumor activity against leukemia L1210, and its solubility is 3 mg/mL in 5% glucose solution. The solubility of Pt(oxalato)(*cis*-dach) is comparable to that of $Pt(NO_3)_2$(dach) and greater than that of $PtCl_2(NH_3)_2$ (1 mg/mL in 5% glucose solution).

Both the amino groups in *cis*-dach are in axial and equatorial bonding, while those of *trans*-dach are in either diaxial or diequatorial bonding. The Newman projection of the platinum complexes of *cis*- and *trans*-dach is shown in Figure 1. The cyclohexane and chelate rings in the

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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Received June 28, 1978

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

0022-2623/78/1821-1318$01.00/0