Biological Assays. The antiovulatory activity of each analogue was determined in Sprague–Dawley rats in a standard assay[20] using a 40% propane-1,2-diol/0.9% saline vehicle. The results (given in Table IV) are expressed as the percentage of (n) rats that did not ovulate at a dose of x μg of analogue. The in vitro histamine-releasing activity of each analogue was determined by using peritoneal cells from male Sprague–Dawley rats in a standard assay,[15] and the results are given as the ED_{50} values expressed in micrograms/milliliter (standard compound 48/80 has an ED_{50} of 0.58 in this assay system). The results are given Table IV.

(20) Vilchez-Martinez, J. A.; Coy, D. H.; Coy, E. J.; Arimura, A.; Schally, A. V. *Endocr. Res. Commun.* **1976**, *3*, 231.

Acknowledgment. We gratefully acknowledge the technical assistance of Ellen Shaw and Irene Brohm for conducting some of the antiovulatory bioassays and Dr. Marven Karten of the Center for Population Research, National Institutes of Health, Bethesda, MD, for arranging the in vitro histamine-release bioassays and the remainder of the antiovulatory assays. The in vitro histamine-release assays were conducted by Drs. William A. Hook and Reuben P. Siraganian of the Clinical Immunology Section, Laboratory of Microbiology and Immunology, National Institute of Dental Research, National Institutes of Health, Bethesda, MD. This work was supported by NIH Contract NO1-HD-4-2832 to D.H.C.

Effect of β-Alkyl Substitution on D-1 Dopamine Agonist Activity: Absolute Configuration of β-Methyldopamine

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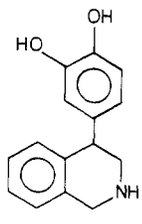
β-Methyldopamine and its enantiomers and racemic β-phenyldopamine were synthesized and evaluated for dopamine D-1 agonist activity. In the dopamine-sensitive adenylate cyclase assay, β-phenyldopamine had about one-sixth the activity of dopamine. Racemic β-methyldopamine was less potent. The absolute configuration of β-methyldopamine was determined to be *R*-(+) and *S*-(−). Evaluation of (*R*)-(+)- and (*S*)-(−)-β-methyldopamine revealed no enantioselectivity for stimulation of adenylate cyclase.

4-(3,4-Dihydroxyphenyl)-1,2,3,4-tetrahydroisoquinoline (**1**) has been found to be a selective dopamine D-1 and DA_1 agonist.[1,2] A related compound, SKF 38393 (**2**), was also found to be a selective dopamine D-1 and DA_1 agonist.[3] Both **1** and **2** incorporate a β-phenyldopamine fragment, and it has been postulated that this fragment may be responsible for the selective dopamine agonist properties of **1** and **2**.[4]



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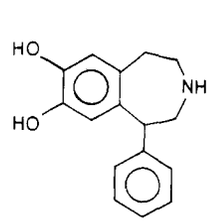

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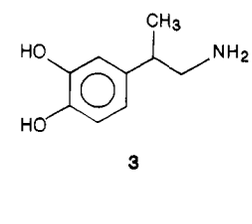

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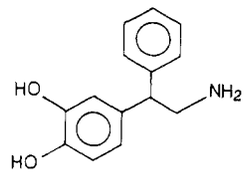

4

In 1978, Goldberg and Kohli[5] stated that no α- or β-substituted dopamine analogue were known that were active in the canine renal artery assay, a model of the vascular DA_1 receptor. Indeed, α-methyldopamine is an extremely weak dopamine agonist. This can probably be attributed to a lack of tolerance by the receptor for steric bulk attached to the α side chain carbon.[6] However, no dopamine agonist data have been reported for simple β-alkyl-substituted dopamines.[7] Therefore, it was decided to investigate the dopamine agonist properties of racemic β-methyldopamine (**3**), its resolved enantiomers, and β-phenyldopamine (**4**).

β-Methyldopamine was previously synthesized by Chavdarian et al.[8] These workers studied the oxidation potential and pressor effects of **3**. In that study, it was found that β-methyldopamine had about half of the pressor effect of dopamine itself. It should be noted that their data did not distinguish between dopaminergic and adrenergic activity.

β-Phenyldopamine (**4**) can be viewed as a partial structure of **1** and **2**. The X-ray crystal structure of

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(3) Setler, P.; Sarau, H.; Zirkle, C.; Saunder, H. *Eur. J. Pharmacol.* **1978**, *50*, 419.
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(6) Nichols, D.; Jacob, J.; Hoffman, A.; Kohli, J.; Glock, D. *J. Med. Chem.* **1984**, *27*, 1701.
(7) Kaiser, C.; Tikam, J. *Medicinal Res. Rev.* **1985**, *5*, 145.
(8) Chavdarian C.; Karashima, D.; Castagnoli, N. *J. Med. Chem.* **1978**, *21*, 548.

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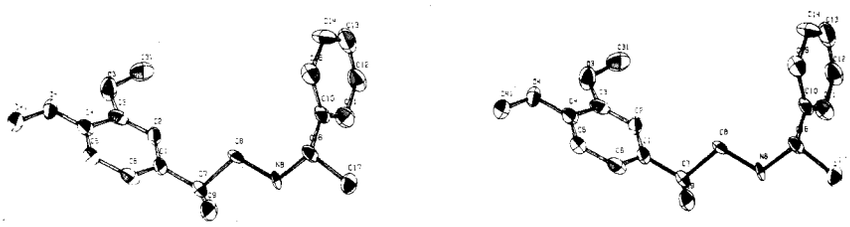


Figure 1. Convergent (cross-eyed viewing) stereopair of the crystal structure of (αS,2R)-(−)-**10a**. Hydrogen atoms have been omitted for clarity.

(*S*)-3′,4′-dihydroxynomifensine shows the phenyl ring to be twisted out of plane with respect to the catechol ring.[9] It was speculated, on the basis of the above comparisons, that β-phenyldopamine might also have selective dopamine D-1 agonist activity.

Chemical Discussion

Racemic β-methyldopamine was synthesized as shown in Scheme I. Methylation of 3,4-dimethoxyphenylacetic acid was effected by treatment of the dianion with methyl iodide. Conversion to the acid chloride, followed by treatment with benzylamine, afforded the amide **7**.

Reduction of **7** was best performed with diborane/THF, providing the *N*-benzylamine **8**. N-Debenzylation of the free base was performed by using Pearlman's catalyst (20% palladium hydroxide on carbon) and shaking with hydrogen at 50 psig.

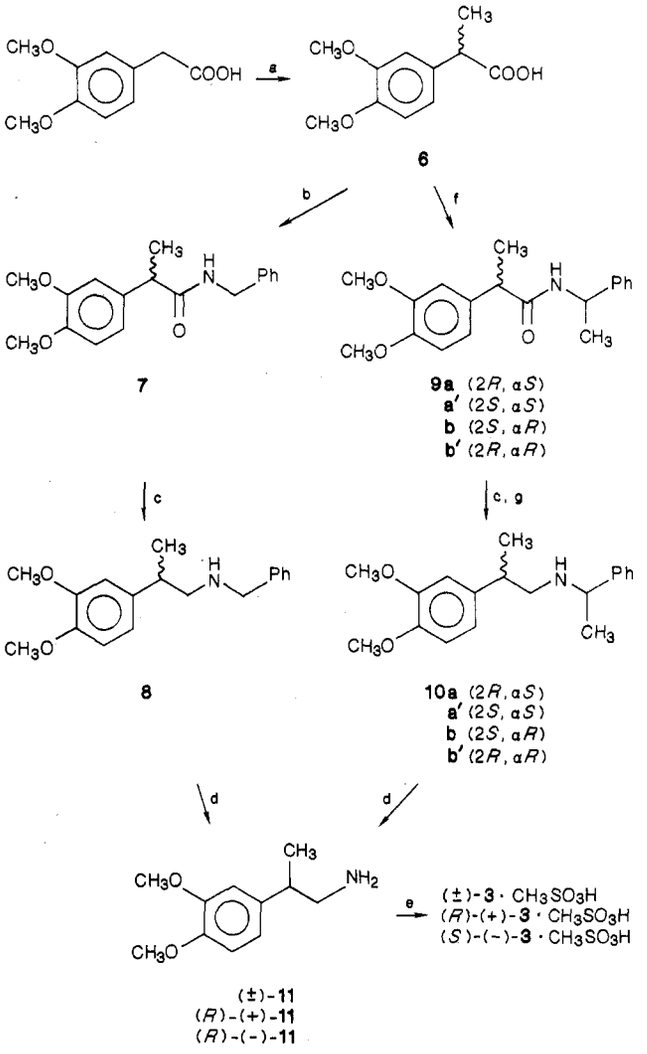
O-Demethylation was performed with 48% hydrobromic acid at reflux. Neither the hydrobromide salt nor the hydrochloride salt[8] of β-methyldopamine could be crystallized. Therefore, the crude hydrobromide salt was converted to the methanesulfonate by adding 1 molar equiv of methanesulfonic acid in ethanol, followed by solvent removal and drying under high vacuum for 24 h. This salt was then crystallized from 2-propanol/ethyl acetate.

The resolution of β-methyldopamine by chromatographic separation of the (*S*)-α-methylbenzyl amides **9a**, **9a′** or of diastereomeric amine mixture **10a**, **10a′** was investigated. The diastereomeric mixture **9a**, **9a′** was prepared from (*S*)-α-methylbenzylamine and **6**. The amides could not be satisfactorily separated by TLC using various solvent systems. Reduction with BH_3/THF provided the diastereomeric mixture of amines **10a**, **10a′**. These could be resolved by TLC. Attempted preparative separation of 1.5 g of **10a**, **10a′** using centrifugal chromatography (chromatotron; 4-mm silica gel rotor) provided a pure sample only of the diastereomer with higher R_f, making it necessary to repeat the process with the diastereomeric amines **10b**, **10b′**. A smaller plate loading of **10a** subsequently allowed purification of each diastereomer without contamination.

The methanesulfonate salts of the resolved diastereomeric amines were easily crystallized, and the diastereomer with higher R_f in **10a**, **10a′** was analyzed by X-ray crystallography. The absolute configuration was found to be (−)-(*S*)-*N*-(α-methylbenzyl)-2(*R*)-(3,4-dimethoxyphenyl)-propylamine (Figure 1), based on the absolute configuration of the starting material ((*S*)-α-methylbenzylamine) used in the synthesis.

Debenzylation using catalytic hydrogenation over 10% Pd/C converted the *N*-(α-methylbenzyl)amines to (*R*)-**11** and (*S*)-**11**. Aqueous 48% HBr at reflux was employed to O-demethylate these to (*R*)-(+)-**3** and (*S*)-(−)-**3**. After conversion to the methanesulfonate salts, the pure enantiomers were recrystallized from 2-propanol/ethyl acetate.

Scheme I[a]



[a] (a) LDA, CH_3I, (b) $SOCl_2$, $PhCH_2NH_2$, (c) BH_3/THF, (d) H_2 Pd/C, (e) 48% HBr, reflux, CH_3SO_3H, (f) $SOCl_2$, (*R*)- or (*S*) $PhCH(CH_3)NH_2$, (g) chromatographic resolution.

β-Phenyldopamine was prepared from ketone **12**. Treatment with trimethylsilyl cyanide, following the procedure of Gassman and Talley,[10] gave the intermediate trimethylsilyl ether of the cyanohydrin. It was originally envisioned that the trimethylsilyl ether of the cyanohydrin could be converted in two steps to **13**; reduction with BH_3/THF to the β-amino alcohol, followed by catalytic hydrogenolysis in acidic media. However, the trimethylsilyl ether was reduced directly to **13** by diborane.

Amine **13** was O-demethylated by reflux in aqueous 48% hydrobromic acid to give **4**. The crude final product was

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Scheme II

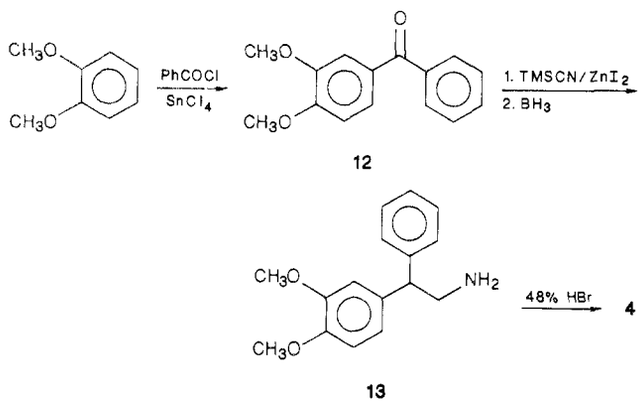

Table I. Percent Stimulation of Rat Retinal Adenylate Cyclase by Test Compounds

compound	concn, μM	% stimulation[a]
dopamine	0.1	31.4 ± 3.4
	1.0	106.4 ± 9.3
	10.0	205.4 ± 10.3
(±)-3	0.1	5.9 ± 4.6
	1.0	−3.5 ± 9.6
	10.0	10.5 ± 1.8
(*R*)-(+)-3	0.1	1.5 ± 10.4
	1.0	6.0 ± 3.2
	10.0	41.0 ± 3.9
(*S*)-(−)-3	0.1	1.6 ± 2.5
	1.0	11.7 ± 3.7
	10.0	39.1 ± 6.3
4	0.1	4.9 ± 2.9
	1.0	16.3 ± 3.6
	10.0	97.1 ± 4.2

[a] The data represent the means ± SEM of three experiments.

recrystallized as the hydrobromide from 2-propanol/ethyl acetate.

Pharmacology Discussion

The compounds were assayed for their ability to stimulate the production of cyclic AMP by rat retinal adenylate cyclase. Retinal membranes have been shown to lack D-2 receptors.[11] Extensive characterization of retinal adenylate cyclase and comparison with cyclase isolated from the brain of a variety of mammalian species have shown that the properties of cyclase from retina and from various regions of the CNS are quite similar.[12] In a previous study[2] we reported that the stimulatory effects of certain dopamine D-1 agonists on rat retinal adenylate cyclase were blocked in a competitive manner by the specific D-1 antagonist SCH 23390. Thus, rat retinal adenylate cyclase appeared to be a convenient model for the dopamine D-1 receptor.

Results and Discussion

As seen in Table I, racemic β-methyldopamine **3** had very low activity in stimulating adenylate cyclase. Surprisingly, the *R* and *S* enantiomers were essentially equipotent in stimulating dopamine-sensitive adenylate cyclase. Both were slightly more active than the racemate, having about one-fifth the activity of dopamine at 10 μM. The most active compound of the series was β-phenyldopamine, which at 0.1–1.0 μM had one-sixth the activity of dopamine and at 10 μM had about half the activity of dopamine.

The activity of β-phenyldopamine may be rationalized by the binding of the free phenyl group to the proposed hydrophobic site on the D-1 receptor,[4,9,13,14] thus enhancing dopamine D-1 agonist activity. Conversely, the decreased activity and the lack of enantioselectivity of β-methyldopamine might be rationalized by the inability of the smaller methyl group to bind adequately to the hydrophobic site. However, the β-methyl group still increases steric bulk and, therefore, may decrease overall affinity for the receptor. However, we are at a loss to explain why both enantiomers are more active than the racemate; the biological assays were repeated on two different occasions with identical results and spcific rotations were reconfirmed on the samples.

It is proposed here that β-phenyldopamine is the essential fragment responsible for the D-1 selectivity of **1** and 3′,4′-dihydroxynomifensine.[3,9] The benzazepine ring of **1** and the tetrahydroisoquinoline of 3′,4′-dihydroxynomifensine may serve to fix the orientation of the phenyl ring and the amine into a conformation that is optimal for dopamine D-1 receptor activation.

Experimental Section

Melting points were determined with a Fisher-Johns apparatus and are uncorrected. NMR spectra were recorded on a Varian FT-80 or XL-200 instrument. Chemical shifts are reported in parts per million with TMS or DSS as the internal reference. The multiplicities are expressed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Chemical-ionization (CI) mass spectra were obtained with a Finnigan 4000 quadrupole spectrometer. Elemental analyses were performed by the Purdue Microanalytical Laboratory and were within ±0.4% of the calculated values unless otherwise noted.

2-(3,4-Dimethoxyphenyl)propanoic Acid (6). Diisopropylamine (2.86 mL, 20.4 mmol) was introduced via a syringe into 90 mL of dry THF under a nitrogen atmosphere. The mixture was cooled to −50 °C and 12.75 mL (20.4 mmol) of 1.6 M *n*-butyllithium in hexane was added. The reaction mixture was then allowed to warm to −20 °C and was stirred for 20 min. A solution of 2-(3,4-dimethoxyphenyl)acetic acid (2 g, 10.2 mmol) dissolved in 10 mL of THF was then added. The reaction mixture was stirred at 25 °C for 50 min, and 0.64 mL (1.46 g, 11 mmol) of methyl iodide was added.

The reaction mixture was stirred overnight and then diluted with 100 mL of water. THF was removed by rotary evaporation, and the aqueous residue was washed with ether (3 × 50 mL). The aqueous solution was then acidified to pH 1 with 6 N HCl and extracted with ether (5 × 70 mL). The organic solution was dried ($MgSO_4$). After filtration and removal of the solvent, the residue was recrystallized from ethyl acetate/hexanes: yield 1.4 g (70%); mp 68–70 °C (lit.[15] mp 62–64 °C); ^1H NMR ($CDCl_3$) δ 6.87 (s, 3, Ar H), 3.87, 3.86 (2 s, 6, CH_3O), 3.77 (q, 1, CH), 1.5 (d, 3, CH_3).

***N*-Benzyl-2-(3,4-dimethoxyphenyl)propanamide (7).** The acid **6** (1.9 g, 9.5 mmol) was dissolved in 10 mL of benzene containing $SOCl_2$ (2 mL, 23 mmol). After the mixture was stirred at reflux for 3 h, the solvents were removed by rotary evaporation, and the crude acid chloride was dissolved in 30 mL of benzene. Benzylamine (2.5 g, 23 mmol) dissolved in 10 mL of benzene was added over a 10-min period and stirring was continued for an additional 15 min. The mixture was then diluted with 50 mL of ether and washed sequentially with 50 mL of water, 50 mL of 1 N HCl, and 50 mL of 1 N NaOH and was then dried ($MgSO_4$). After filtration and removal of the solvent by rotary evaporation, the crude product was recrystallized from ethyl acetate/hexanes: yield 1.64 g (57.8%); mp 116–117 °C; ^1H NMR ($CDCl_3$) δ 7.20 (m, 5, Ar H), 6.81 (s, 3, Ar H), 5.74 (br s, 1, NH), 4.38 (d, 2, CH_2),

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3.85, 3.83 (2 s, 6, CH_3O), 3.55 (q, 1, CH), 1.52 (d, 3, CH_3). Anal. ($C_{17}H_{21}NO_3$) C, H, N.

***N*-Benzyl-2-(3,4-dimethoxyphenyl)propylamine Methanesulfonate (8).** Amide **7** (1 g, 3.22 mmol) was dissolved in 50 mL of THF, and 6 mL (6 mmol) of 1 M BH_3/THF was added. The mixture was held at reflux for 2 h. After removal of THF by rotary evaporation, the residue was redissolved in 40 mL of 6 N HCl and held at reflux for 2 h. After cooling, the aqueous solution was washed with ether (3 × 50 mL), basified to pH 10 with 10% NaOH, and extracted with ether (4 × 50 mL). The organic solution was washed with 100 mL of saturated brine and dried ($MgSO_4$). After removal of solvent, 900 mg of free base was obtained (yield 98%); this was converted to the methanesulfonate salt by addition of 1 equiv of methanesulfonic acid: mp 160–162 °C; ^1H NMR ($CDCl_3$, methanesulfonate salt) δ 8.2 (br s, 2, NH_3^+), 7.38 (s, 5, Ar H), 6.75 (m, 3, Ar H), 4.14 (m, 2, CH_2), 3.83, 3.81 (2 s, 6, CH_3O), 2.95 (m, 3, $CHCH_2$), 2.74 (s, 3, CH_3SO_3), 1.34 (d, 3, CH_3). Anal. ($C_{18}H_{27}NO_5S$) C, H, N.

(±)-2-(3,4-Dimethoxyphenyl)propylamine Hydrochloride (11). The hydrochloride salt of *N*-benzyl-2-(3,4-dimethoxyphenyl)propylamine (**8**; 1.4 g, 4.35 mmol) was dissolved in 45 mL of methanol. To the mixture was added a slurry of 200 mg of 10% palladium/carbon in 5 mL of water, and the mixture was shaken with hydrogen at 50 psig for 48 h. The mixture was filtered through Celite, and the solvents were removed by rotary evaporation. The crude product was recrystallized from ethanol/ether: yield 760 mg, (75.2%); mp 205–207 °C (lit.[8] mp 202–204 °C); ^1H NMR (D_2O) δ 6.68 (m, 3, Ar H), 3.65, 3.61 (2 s, 6, CH_3O), 2.97 (m, 3, $CHCH_2$), 1.14 (d, 3, CH_3).

(±)-2-(3,4-Dihydroxyphenyl)propylamine Methanesulfonate (3). Compound **11** (0.4 g, 1.73 mmol) was dissolved in 3.5 mL of 48% HBr. The mixture was held at reflux under a nitrogen atmosphere for 1 h. After cooling, the excess HBr was removed by rotary evaporation. The residue was converted to the methanesulfonate salt by addition of methanesulfonic acid (0.166 g, 1.73 mmol) in 2 mL of absolute ethanol, followed by rotary evaporation to remove ethanol, and drying under high vacuum (0.5 mm for 24 h). The crude salt was recrystallized from 2-propanol/ethyl acetate: yield 300 mg (64.5%); mp 143–146 °C; ^1H NMR (D_2O) δ 6.83 (m, 3, Ar H), 3.11 (m, 3, $CHCH_2$), 2.81 (s, 3, CH_3SO_3), 1.28 (d, 3, CH_3). Anal. ($C_9H_{17}NO_5S$) C, H, N.

***N*-((*S*)-α-Methylbenzyl)-2(*RS*)-(3,4-dimethoxyphenyl)propylamine (10a,10a').** Acid **6** (2.0 g, 9.5 mmol) was stirred at reflux with $SOCl_2$ (5 mL, 25.7 mmol) for 2 h. Benzene and excess thionyl chloride were removed by rotary evaporation. The crude acid chloride was dissolved in 10 mL of benzene and added to a solution of 1.5 g (12.4 mmol) of (*S*)-α-methylbenzylamine (Aldrich) in 20 mL of benzene containing 2 mL of pyridine. The reaction mixture was allowed to stir for 15 min and was washed with 50 mL of water, 50 mL of 1 N HCl, and finally 50 mL of 5% Na_2CO_3. The organic solution was dried ($MgSO_4$).

After filtration and removal of the solvent, the crude diastereomeric amide mixture (**9a**, **9a'**) was dissolved in 20 mL of dry THF. To the amide solution was added 25.5 mL (25.5 mmol) of 1 M BH_3/THF. The reaction mixture was stirred for 72 h at 25 °C. The THF was removed by rotary evaporation and the complex was decomposed by addition of 20 mL of methanol and 1 mL of concentrated HCl, followed by stirring at reflux for 2 h. After cooling, the solvents were removed by rotary evaporation. The residue was dissolved in 50 mL of 1 N HCl and washed with ether (2 × 50 mL). The aqueous solution was basified to pH 10 with concentrated NH_4OH, then extracted with CH_2Cl_2 (3 × 50 mL), and dried ($MgSO_4$). The organic solution was filtered and concentrated to yield 2.73 g of the diastereomeric amines **10a**, **10a'**.

***N*-((*R*)-α-Methylbenzyl)-2(*RS*)-(3,4-dimethoxyphenyl)propylamine (10b, 10b').** Acid **6** (1.2 g, 5.71 mmol) was converted to the mixture of **9b** and **9b'**, following the procedure for **9a** but with (*R*)-α-methylbenzylamine, and this was reduced to afford a quantitative yield (1.64 g) of **10b**, **10b'**.

Resolution. The mixture of **10a** and **10a'** (1.5 g) was resolved by centrifugal chromatography (chromatotron). A 4-mm silica gel rotor under a N_2/NH_3 atmosphere was employed, with CH_2Cl_2 as the eluting solvent. After careful fractionation, 600 mg of the faster eluting major band was obtained. This was converted to the methanesulfonate salt: mp 134–136 °C; $[\alpha]^{20}_D$ −23.8 °C (c 0.92, EtOH). The process was repeated with 1 g of the mixture of **10b** and **10b'** under the same conditions, to yield 200 mg of the faster eluting band. This base was converted to the methanesulfonate salt by addition of 1 equiv of methanesulfonic acid and recrystallization: mp 134–136 °C; $[\alpha]^{20}_D$ +22.5° (c 1, EtOH); ^1H NMR (free base, $CDCl_3$) δ 7.30 (s, 5, Ar H), 6.75 (m, 3, Ar H), 3.85 (s, 6, CH_3O), 2.75 (m, 4, 2 Ch, CH_2), 2.50 (br s, 1, NH), 1.38 (d, 2, CH_3), 1.22 (d, 2, CH_3). Anal. ($C_{20}H_{28}NO_5S$) C, H, N.

(*R*)-(+)-2-(3,4-Dimethoxyphenyl)propylamine Hydrochloride ((*R*)-(+)-11). Pure (α*S*,2*R*)-**10a**·CH_3SO_3H (257 mg, 0.65 mmol) was dissolved in 10 mL of methanol. Pearlman's catalyst (Aldrich) (50 mg) was added and the mixture was shaken at 50 psig H_2 for 16 h. After removal of the catalyst by filtration, the solvent volume was reduced to 5 mL and was chromatographed through an anion-exchange column (chloride form). After removal of the solvent, the residue was recrystallized from ethanol/ether: yield 116 mg (77%); mp 184–186 °C; $[\alpha]^{25}_{578}$ +26.89° (c 0.6, H_2O).

(*S*)-(−)-2-(3,4-Dimethoxyphenyl)propylamine Hydrochloride ((*S*)-(−)-11). To a solution containing (α*R*,2*S*)-**10b** (150 mg, 0.50 mmol) dissolved in 25 mL of methanol was added 10 mg of Pearlman's catalyst. The mixture was shaken at 50 psig H_2 for 24 h. After removal of the catalyst by filtration, the methanol was removed by rotary evaporation, and the crude free base was converted to the HCl salt by addition of ethanolic HCl and recrystallized from ethanol/ether: yield 75 mg (65%); mp 185–187 °C; $[\alpha]^{25}_{578}$ −26.94° (c 0.5, H_2O).

(*R*)-(+)-2-(3,4-Dihydroxyphenyl)propylamine Methanesulfonate (3). (*R*)-(+)-**11**, free base (86 mg, 0.44 mmol) was demethylated to (*R*)-(+)-**3** following the procedure for preparation of the HBr salt of racemic **3**. The residue was converted to the methanesulfonate salt by addition of methanesulfonic acid (42 mg, 0.44 mmol), and the crude salt was recrystallized from 2-propanol/ethyl acetate: yield 29 mg (25%); mp 142–145 °C; $[\alpha]^{25}_{578}$ +21.5° (c 0.4, H_2O); CI-MS, base peak, 97 (M + 1 − NH_3), 151 (60%), M + 1, 168 (7%).

(*S*)-(−)-2-(3,4-Dihydroxyphenyl)propylamine Methanesulfonate Salt 3. Amine salt (*S*)-(−)-**11** (75 mg, 0.32 mmol) was converted to (*S*)-(−)-**3**, following the procedure for (+)-**3**: yield 34 mg (40.5%); mp (mp 143–145 °C; $[\alpha]^{25}_{578}$ −21.3% (c 0.4, H_2O); CI-MS, base peak, 97 (M + 1 − NH_3); 151 (60%); M + 1, 168 (7%).

3',4'-Dimethoxybenzophenone (12). Veratrole (15.8 g, 100 mmol) and benzoyl chloride (14.1 g, 100 mmol) were dissolved in 150 mL of CH_2Cl_2 and cooled to 0 °C. Tin(IV) chloride (27.8 g, 120 mmol) was added dropwise to maintain the temperature between 0 and 10 °C. The reaction mixture was stirred at 25 °C for 0.5 h and was then heated at reflux for 2 h, followed by stirring at 25 °C for 6 h. The mixture was poured over 70 g of ice, and the phases were separated. The organic phase was washed with 6 N HCl (8 × 125 mL) and 100 mL of water and dried ($MgSO_4$). This solution was passed through a short (30 g) silica gel pad to remove residual tin salts. After solvent removal, the residue was recrystallized from methanol: yield 15.95 g (65.9%); mp 100–101 °C (lit.[16] mp 100 °C).

2-(3,4-Dimethoxyphenyl)-2-phenylethylamine Hydrochloride (13). A solution of 3',4'-dimethoxybenzophenone (**12**; 0.5 g, 2.1 mmol) was stirred at 25 °C for 16.0 h with 0.3 mL of trimethylsilyl cyanide (0.230 g, 2.31 mmol) in 20 mL of CH_2Cl_2 containing 50 mg of ZnI_2. The mixture was washed with 50 mL of water and then dried ($MgSO_4$). After removal of solvent by rotary evaporation, the crude (trimethylsilyl)cyanohydrin was dissolved in 10 mL of THF. To the solution was added 1 M BH_3/THF (4 mL, 4 mmol), and the mixture was stirred at reflux under a nitrogen atmosphere for 16 h. The solvent was removed by rotary evaporation, and the residue was redissolved in 20 mL of methanol containing 1 mL of concentrated HCl and stirred at reflux for 16 h to decompose the borane–amine complex. The solvents were removed by rotary evaporation, and the residue was redissolved in 20 mL of water. The aqueous solution was extracted with ether (2 × 20 mL), basified with concentrated NH_4OH, extracted with CH_2Cl_2 (2 × 20 mL), and dried ($MgSO_4$). After filtration and solvent removal, 20 mg of free base was obtained. The base was converted to the HCl salt with ethanolic HCl and recrystallized from ethanol/ether: yield 0.241 g (40.7%); mp 107–110 °C (lit.[17] mp (methanol/ethyl acetate) 143–145 °C, lit.[18]

(16) Tarbell, D.; Price, J. *J. Org. Chem.* **1957**, *22*, 245.

mp 173–174 °C); ^{1}H NMR ($CDCl_3$, free base) δ 7.25 (m, 5, Ar H), 6.78 (m, 3, Ar H), 3.87 (m, 1, CH), 3.84, 3.83 (2 s, 6, CH_3O), 3.30 (m, 2, CH_2), 2.04 (br s, 2, NH_2). Anal. ($C_{16}H_{20}NClO_2$) C, H, N.

2-(3,4-Dihydroxyphenyl)-2-phenylethylamine Hydrobromide (4). A solution of compound **13**·HCl (0.08 g, 0.27 mmol) in 1 mL of 48% HBr was stirred for 1.5 h at reflux under a nitrogen atmosphere. After removal of the HBr by rotary evaporation, the residue was recrystallized from 2-propanol/ethyl acetate: yield 55 mg (65%); mp 232–235 °C; ^{1}H NMR (D_2O) δ 6.69 (s, 5, Ar H), 6.33 (m, 3, Ar H), 4.47 (dd, 1, CH), 4.05 (d, 2, CH_2). Anal. ($C_{14}H_{16}BrNO_2$) C, H, N.

X-ray Analysis. The X-ray analysis of a single crystal of the pure ($\alpha S,2R$)-**10a**·CH_3SO_3H diastereomer was performed.

Crystal data: $C_{19}H_{25}NO_2{\cdot}CH_3SO_3H$, MW = 395.65, orthorhombic, a = 12.73 (1) Å, b = 9.134 (4) Å, c = 17.881 (8) Å, V = 2080 (2) Å^3, Z = 4, ρ_{calcd} = 1.27 g/cm^3, $F(000)$ = 848, μ(Cu Kα) = 15.28, space group $P2_12_12_1$ from systematic absences.

Data Collection. Crystallographic data were collected with Cu Ka X-rays and a monochromator on a Nicolet P3 four-circle diffractometer, with the θ–2θ scan technique out to a 2θ of 116.0°. A variable scan rate was used with a maximum of 29.30°/min and a minimum of 7.23°/min. The scan range was from 1.2° < Kα_1 to 1.2° > Kα_2; the time that backgrounds at both ends of the scan range was counted equivalent to the scan time. Three standard reflections were measured every 50 reflections.

Structure Analysis. Twenty-two reflections were rejected as systematically absent of the 1649 reflections collected, leaving 1627 unique reflections, of which 1326 met the condition of $F_o > 5\sigma(F_o)$ and were considered observed. The structure was solved by using the MULTAN80 program and refined by SHELX76 to a final R of 0.0789 with the hydrogens fixed in their calculated positions. A final difference map showed no peaks greater than 0.40 e/Å^3. Absolute configuration is (*S*)-(−)-*N*-(α-methylbenzyl)-2(*R*)-(3,4-dimethoxyphenyl)propylamine (Figure 1.).

Pharmacology. The procedure for the dopamine-sensitive rat retinal adenylate cyclase assay was performed as follows: Rat retinas were homogenized in 150 vol/wt of 2.0 mM Tris·HCL,pH 7.4, with 2 mM EDTA with a Teflon–glass homogenizer. Each reaction mixture contained the following final concentrations in a volume of 0.2 mL: 2 mM $MgSO_4{\cdot}7\ H_2O$, 0.5 mM EGTA, 1 mM IBMX, 0.01 mM GTP, 80 mM Tris·HCl (pH 7.4), 0.5 mM ATP with approximately 5 × 10^6 DPM [^{32}P]ATP and 20–30 μg of retinal homogenate protein. Following an incubation of 20 min at 30 °C, the reaction was terminated by adding 200 μL of a solution containing 1% SDS, 20 mM ATP, 0.7 mM cyclic AMP with 1.0 × 10^4 DPM [^{3}H]cyclic AMP in 80 mM Tris·HCl, pH 7.4, and heating to 85 °C for 2 min. Cyclic AMP was isolated from the mixture by using the column chromatographic technique of Salomon.[19]

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Supplementary Material Available: The atom locations and temperature factors for the X-ray determination of **10a** (2 pages) are available. Ordering information is given on any current masthead page.

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Streptonigrin and Lavendamycin Partial Structures. Probes for the Minimum, Potent Pharmacophore of Streptonigrin, Lavendamycin, and Synthetic Quinoline-5,8-diones

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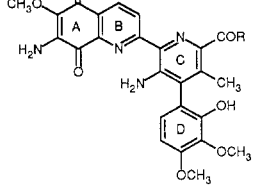
The preparation and evaluation of 7-amino-5,8-dioxo-2-(2′-pyridyl)quinoline-6′-carboxylic acid (**5a**) and 7-amino-2-(2′-aminophenyl)-5,8-dioxoquinoline-5′-carboxylic acid (**6a**) constituting potential minimum, potent pharmacophores of streptonigrin (**1a**) and lavendamycin (**2a**), two structurally related naturally occurring antitumor antibiotics, are detailed. In contrast to observations associated with streptonigrin and lavendamycin in which the C-ring C-6′ carboxylic acid *potentiates* the antitumor, antimicrobial, and cytotoxic properties of the naturally occurring, substituted 7-aminoquinoline-5,8-dione AB ring systems, the C-6′/C-5′ carboxylic acid of **5a**/**6a** *diminishes* the observed antimicrobial and cytotoxic properties of the 2-(2′-pyridyl)- and 2-(2′-aminophenyl)-7-aminoquinoline-5,8-diones. A direct comparison of the antimicrobial and cytotoxic properties of a complete set of streptonigrin and lavendamycin partial structures is detailed in efforts to define the role peripheral substituents play in potentiating the biological properties of the naturally occurring and synthetic agents bearing the 7-aminoquinoline-5,8-dione AB ring system and in efforts to define the minimum, potent pharmacophore of the naturally occurring antitumor antibiotics. The relationship of these observations to a chemical mechanism of cellular toxicity is discussed.

Streptonigrin (**1a**), a highly substituted and highly functionalized 7-aminoquinoline-5,8-dione first isolated from *Streptomyces flocculus*,[2-7] has been shown to possess potent cytotoxic properties, confirmed broad spectrum antitumor activity, and in vitro and in vivo antiviral properties[19] and to display potent, broad spectrum antimicrobial properties.[8-20] Early detailed investigations[14-18] defined the broad spectrum antitumor activity of streptonigrin against sarcoma 180, mammary adenosarcoma 755, Lewis lung carcinoma, Ridgway and Wagner osteogenic carcinoma, Harding–Passey melanoma, Walker 256 car-



1a, R = OH Streptonigrin
1b, R = OCH_3 Streptonigrin methyl ester
1c, R = $NHNH_2$ Streptonigrin hydrazide

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