the "downward" direction is not enough to stabilize the agonist conformation of (S)-6, considering that this compound requires 2.4 kcal/mol in conformational energy to acquire the active conformation (see above). Instead, the antagonist conformation, which requires less energy (0.7 kcal/mol), is employed. In contrast, the N-propyl group in the "downward" direction and the methylene group in the "upward" direction in (R)-6 suffice to stabilize its agonist conformation. If the lipophilicity of the N-alkyl groups in (S)-6 is increased by employing the n-butyl analogue (postsynaptically active),[9] the energy requirement for the conformational rearrangement of (S)-6 into its agonist conformation may be fulfilled. An additional factor explaining the postsynaptic agonism of the n-butyl analogue of (S)-6 may possibly be decreased postsynaptic antagonism due to N-alkyl sensitivity of postsynaptic blockage. This was shown to be the case for the N,N-di-n-butyl analogue of compound 8.[38] The impact of the N-alkyls on the agonist effects may be interpreted as an effect upon the intrinsic activity at the receptor level. Still another way to increase the intrinsic activity, at least postsynaptically, is represented by the catechol (S)-20 compared to (S)-6.[27] Since catechols are known to also stimulate D1 receptors,[1] this raises the possibility that the increased postsynaptic effects of these catechols may partly be due to D1 stimulation.[27]

Conclusions

The spatial relationships between the hydroxyl group, the aromatic ring, the nitrogen atom, and the nitrogen lone pair (or in the case of a protonated nitrogen atom, the NH bond) required for activation of central pre- and postsynaptic DA receptors seem to be identical or at least very similar. This implies that presynaptic selectivity can not be understood in terms of different geometric fits to the two receptor types. For the compounds studied in this work the determining factors for activity and selectivity are (i) the properties of the N-substituents, i.e., lipophilicity, steric requirements, conformational probabilities, and directionality ("upward"/"downward"); (ii) the conformational energy required for flexible molecules like 3PPP (6) to acquire a "correct" geometry; and (iii) the degree of aromatic hydroxylation.

The receptor interaction model presented here, which is based on the McDermed receptor concept, on superimpositions of structures calculated by molecular mechanics and on conformational analysis of N-alkyl substituents suggests that the piperidine ring is equivalent to a methyl group in its interaction with pre- and postsynaptic receptors. This hypothesis led to the prediction of presynaptic selectivity for compound 17, which was also observed in subsequent testing.

Compound 6 was first reported to be a DA autoreceptor selective agonist in its racemic form. Later resolution and testing of the pure enantiomers revealed that (S)-6 has a dual action. It stimulates the high-sensitive autoreceptors and blocks the low-sensitive postsynaptic receptors. Comparisons with rigid structures having either agonistic or antagonistic properties and conformational analysis of (S)-6 led to the conclusion that this compound is acting as an agonist in one rotameric form and as an antagonist in another rotameric form. Neither of these conformations is an energy minimum for the isolated molecule. The presynaptic selectivity for (S)-6 and the nonselectivity of (R)-6 are suggested to be due to the different N-alkyl properties in the "upward" and "downward" directions of these compounds in their "agonist conformations" and the conformational energy necessary to acquire these conformations. The proposed receptor interaction model may be further refined through similar analysis work for other classes of molecules active at central pre- and postsynaptic DA receptors.

Acknowledgment. We gratefully acknowledge Dr. Kjell Svensson and his staff for performing the additional behavioral studies needed to make Table I complete. We also thank Dr. Stephan Hjorth for recalculation of data from previous experiments, Miss Boel Göransson for help with the illustrations, and Dr. Robert E. Carter for linguistic criticism. H.W. acknowledges a Fogarty International Postdoctoral Fellowship with the aid of which part of this work was completed. This work was supported by grants from the Swedish Natural Science Research Council and the Swedish Medical Research Council.

(38) Svensson, K.; Carlsson, A.; Johansson, A. M.; Arvidsson, L.-E.; Nilsson, J. L. G., *J. Neural Transm.* **1986**, 65, 29.

Synthesis and Dopaminergic Binding of 2-Aryldopamine Analogues: Phenethylamines, 3-Benzazepines, and 9-(Aminomethyl)fluorenes

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A series of 2-aryldopamine analogues were synthesized and evaluated for their effects on D_1 and D_2 dopamine receptors. The 2-phenyldopamine and 6-phenylbenzazepine analogues exhibited weak binding to both D_1 and D_2 receptors. The 9-(aminomethyl)fluorenes also exhibited weak D_2 binding; however, 2,5,6-trihydroxy-9*H*-fluorene-9-methanamine (4b) exhibited D_1 binding comparable to apomorphine. The binding activity has been correlated with the calculated torsion angle of the biphenyl portion of these molecules. Good D_1 dopamine binding occurs when the aromatic rings approach coplanarity; poor binding occurs when the aromatic rings are orthogonal.

The simplest example of a 2-aryldopamine is 6-(2-aminoethyl)[1,1'-biphenyl]-2,3-diol (1a, 2-phenyldopamine) in which the two aromatic rings of the biphenyl system are not part of a fixed ring system. This compound has been reported to be a very weak stimulator of dopamine-sensitive adenylate cyclase (D_1 dopamine receptor activity)[2] and a potent inhibitor of dopaminergic D_2 agonists in brain

(1) (a) Department of Medicinal Chemistry. (b) Department of Molecular Pharmacology.

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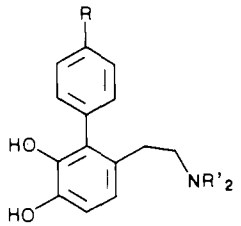
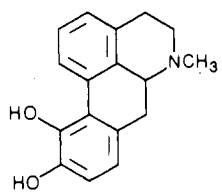


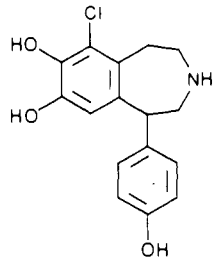
1a, R = H; R' = H
b, R = H; R' = *n*-Pr
c, R = OH; R' = H
d, R = OH; R' = *n*-Pr



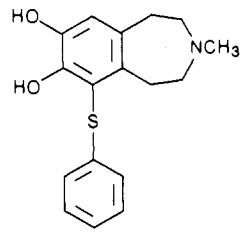
2a

striatum.[3] A more complex example of a 2-aryldopamine is the aporphine alkaloid apomorphine (**2a**) in which the rigid ring system holds the two aromatic rings in a fixed relationship. Apomorphine is a potent mixed D_1/D_2 mixed agonist/antagonist in dopaminergic systems.[4]

Fenoldopam (**2b**, SK&F 82526) is a potent D_1 agonist renal vasodilator.[5] While fenoldopam is not a 2-aryldopamine, it is an aryldopamine analogue in which, in the crystalline state at least, the aromatic rings are not coplanar.[5] Benzazepine **2c** (SK&F 83742), a potent D_1/D_2



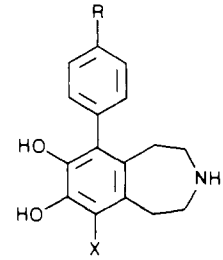
2b



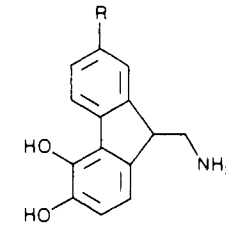
2c

dopamine antagonist,[6] is also an aryldopamine. However, in this case, the interposition of a sulfur atom between the two aromatic rings allows considerable latitude in their stereo relationship.

Thus, in order to investigate the stereo requirements of 2-aryldopamines, we have synthesized analogues with, in some cases, a nonrigid aromatic ring and, in others, a forced coplanarity. Therefore, we have prepared a series of substituted 2-arylphenethylamines (**1a–d**), a series of substituted 6-arylbenzazepines (**3a–d**), and two substituted 9-(aminomethyl)fluorenes (**4a,b**) and evaluated their effects on dopamine receptors. We chose chloro and hydroxy substituents based on our previous work with fenoldopam[7] in which increased D_1 potency and decreased CNS activity were produced with these substituents present. The *N,N*-di-*n*-propyl substituted 2-aryldopamines



3a, R = H; X = H
b, R = H; X = Cl
c, R = OH; X = H
d, R = OH; X = Cl



4a, R = H
b, R = OH

were prepared because of Goldberg's discovery[8] of the potent D_2 activity of *N,N*-di-*n*-propyldopamine.

Chemistry. Initially, we prepared 6-(2-aminoethyl)-[1,1'-biphenyl]-2,3-diol (**1a**)[9] and 2,3,4,5-tetrahydro-6-phenyl-1*H*-3-benzazepine-7,8-diol (**3a**) as outlined in Scheme I. Chloromethylation of 2,3-dimethoxybiphenyl (**5**)[10] proceeded regioselectively in the 4-position, as has been observed with other 3-substituted veratroles.[11] The monochloromethylated compound (**6a**) was readily converted to nitrile **7a**, which after catalytic reduction and demethylation with boron tribromide gave **1a**. Chloromethylation of **5** under more vigorous conditions produced the bis(chloromethyl) compound **9**, which was converted to the dinitrile (**10**). Catalytic hydrogenation of **10** produced benzazepine **11a** in very low yield; demethylation of **11a** afforded catechol **3a**.

In view of the poor yield for the above cyclization reaction and the nongenerality of the overall sequence, we investigated alternate methods of preparing 2-arylphenethylamines and 6-arylbenzazepines.

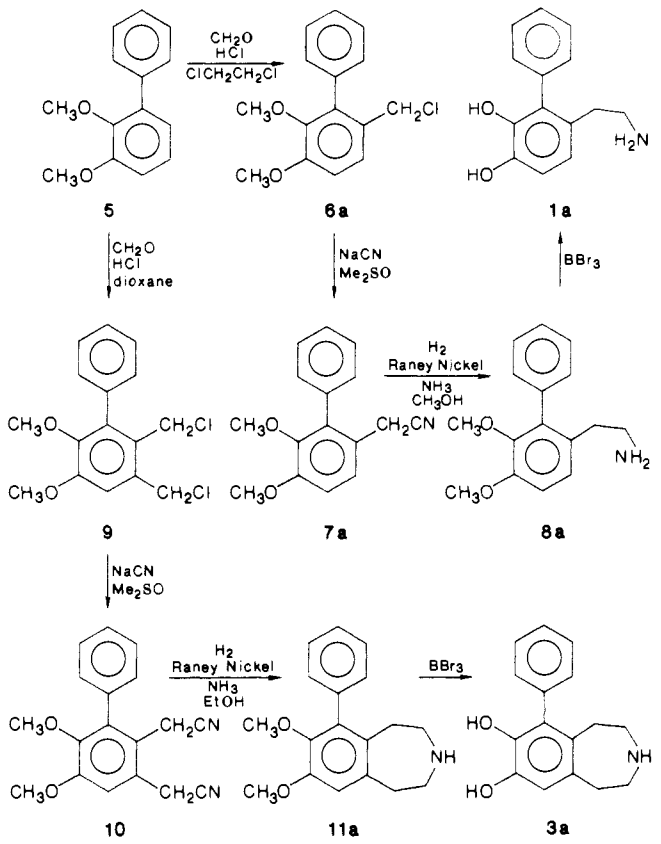
We developed a synthesis (Scheme II) of 2-arylphenethylamines (**8**) from 2-(2-aryl-3,4-dimethoxyphenyl)-4,4-dimethyl-2-oxazolines (**14**) prepared by the method of Meyers.[12] The benzoic acids (**16**) were formed by basic hydrolysis of the quaternary oxazolinium iodides (**15**) and then reduced to the benzyl alcohols (**17**) and converted to the benzyl chlorides (**6**). The benzyl chlorides were then converted to amines (**8**) via the nitriles (**7**) as described above. The *N,N*-di-*n*-propylamines (**18a,b**) were prepared by reductive alkylation with propionaldehyde. Demethylation with boron tribromide produced the 2-aryldopamines (**1a–d**).

We feel that this is a versatile synthesis as virtually any 2-aryl substituent can be introduced via the appropriate Grignard reagent and the overall yield is quite good. Upon completion of this work a report[13] appeared describing an analogous synthesis of **14c** from **13**, which was used as an intermediate in the synthesis of 8-arylisoquinolines.

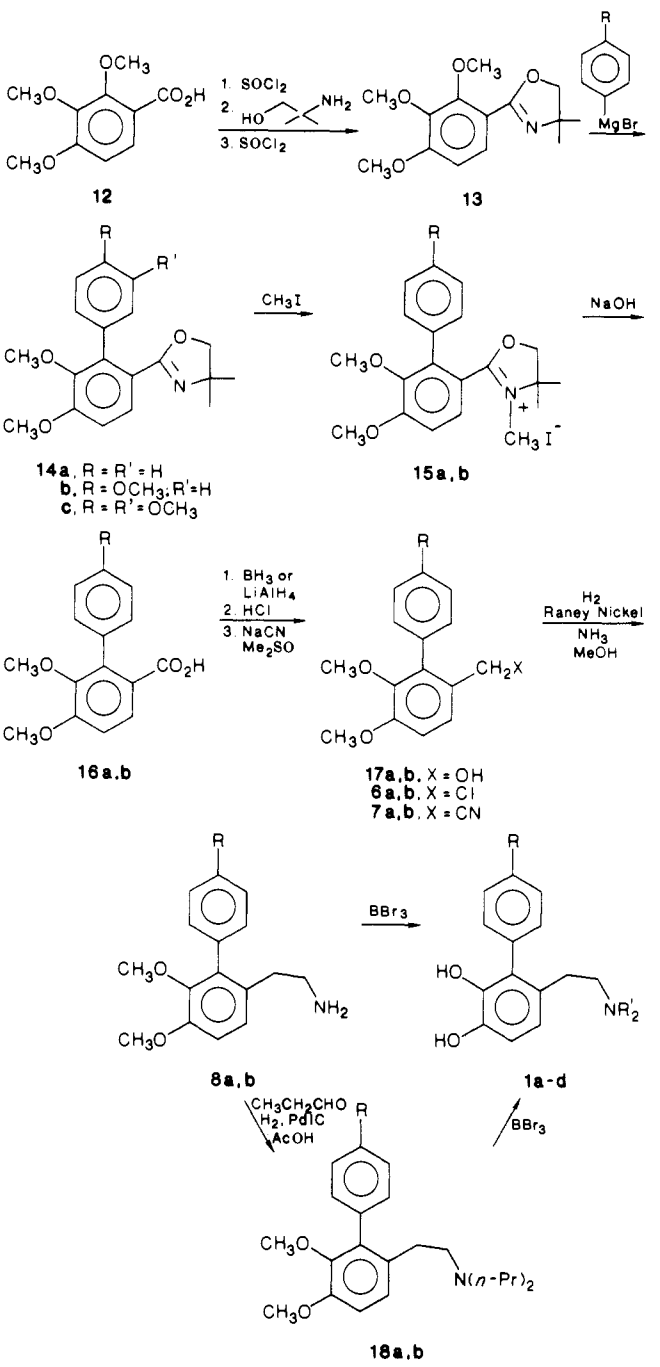
The required 6-arylbenzazepines (**3a–d**) were obtained from the 2-arylphenethylamines (**8**) as outlined in Scheme III. Thus, **8** was converted to chloroacetamides (**19**), which were photolyzed using the method of Witkop[14] to produce

(2) Sheppard, H.; Burghardt, C. R. *Mol. Pharmacol.* **1974**, *10*, 721. *Cyclic Nucleotides in Disease*; Weiss, B., Ed.; University Park Press: Baltimore, MD, 1974; p 117.
(3) Seeman, P. *Pharmacol. Rev.* **1981**, *32*, 229.
(4) Kaiser, C.; Jain, T. *Med. Res. Rev.* **1985**, *5*, 145.
(5) Weinstock, J.; Wilson, J. W.; Ladd, D. L.; Brenner, M.; Ackerman, D. M.; Blumberg, A. L.; Hahn, R. A.; Hieble, J. P.; Sarau, H. M.; Wiebelhaus, V. D. *Dopamine Receptors*; Kaiser, C., Kebabian, J. W., Eds.; American Chemical Society: Washington, DC, 1983; pp 157–169.
(6) Kaiser, C.; Ali, F. E.; Bondinell, W. E.; Brenner, M.; Holden, K. G.; Ku, T. W.; Oh, H.; Ross, S. T.; Yim, N. C. F.; Zirkle, C. L., Hahn, R. A.; Sarau, H. M.; Setler, P. E.; Wardell, J. R., Jr. *J. Med. Chem.* **1980**, *23*, 975.
(7) Weinstock, J.; Wilson, J. W.; Ladd, D. L.; Brush, C. K.; Pfeiffer, F. R.; Kuo, G. Y.; Holden, K. G.; Yim, N. C. F.; Hahn, R. A.; Wardell, J. R., Jr.; Tobia, A. J.; Settler, P. E.; Sarau, H. M.; Ridley, P. T. *J. Med. Chem.* **1980**, *23*, 973.
(8) Kohli, J. D.; Weder, A. B.; Goldberg, L. I.; Ginos, J. Z. *J. Pharmacol. Exp. Ther.* **1980**, *213*, 370.
(9) Although biological data have been reported for this compound, we are unaware of a published synthesis.
(10) Bruce, J. M.; Sutcliffe, F. K. *J. Chem. Soc.* **1955**, 4435.
(11) Kaiser, C.; Burger, A. *J. Am. Chem. Soc.* **1957**, *79*, 4365. Parulkar, A.; Burger, A.; Aures, D. *J. Med. Chem.* **1966**, *9*, 738.
(12) Meyers, A. I.; Mihelich, E. D. *J. Am. Chem. Soc.* **1975**, *97*, 7383.
(13) Patel, H. A.; MacLean, D. B. *Can. J. Chem.* **1983**, *61*, 7.
(14) Yonemitsu, O.; Okuno, Y.; Kanaoka, Y.; Karle, I. L.; Witkop, B. *J. Am. Chem Soc.* **1968**, *90*, 6522.

Scheme I



Scheme II



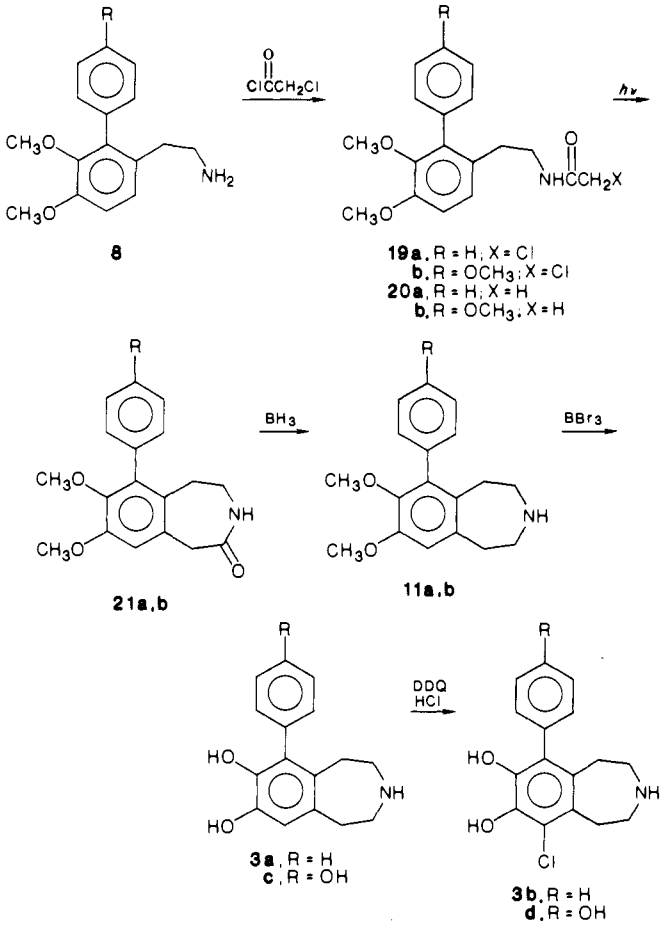
lactams **21** along with considerable amounts of reduced acetamides (**20**) and other byproducts. Borane reduction of **21** produced benzazepines **11**, which were demethylated with boron tribromide to yield **3**. The chlorinated compounds **3b** and **3d** were prepared[6] by converting **3** to the free bases followed by oxidation to the quinones with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in the presence of excess hydrogen chloride.

We also investigated two unsuccessful methods for preparing 6-aryl-3-benzazepines (Scheme IV) that also failed when applied to the synthesis of 8-phenylisoquinolines.[13] Coupling[15] of 4-methoxyphenylmagnesium bromide with bromobenzazepine **22a**[16] in the presence of dichloro[bis(triphenylphosphine)]nickel(II) or with **22b** (prepared as an oil by refluxing **22c** with benzyl bromide and K_2CO_3 in acetone) in the presence of bis(acetylacetonato)nickel(II) produced only reduced benzazepines **24a** and **24b** and 4,4′-dimethoxybiphenyl. Cyclization of *N*-benzyl acetal **25a** with a cold 1:1 mixture of sulfuric and acetic acids produced **27**, presumably via a second cyclization of **26a**. Similar double cyclizations have been reported[17] in the literature. Cyclization of debenzylated acetal **25b** with 18 N sulfuric acid produced **26b**. Attempts to convert **26b** to **11b** (catalytic hydrogenation; borane reduction; conversion to the benzyl chloride with $SOCl_2$ followed by Zn/AcOH reduction) were unsuccessful.

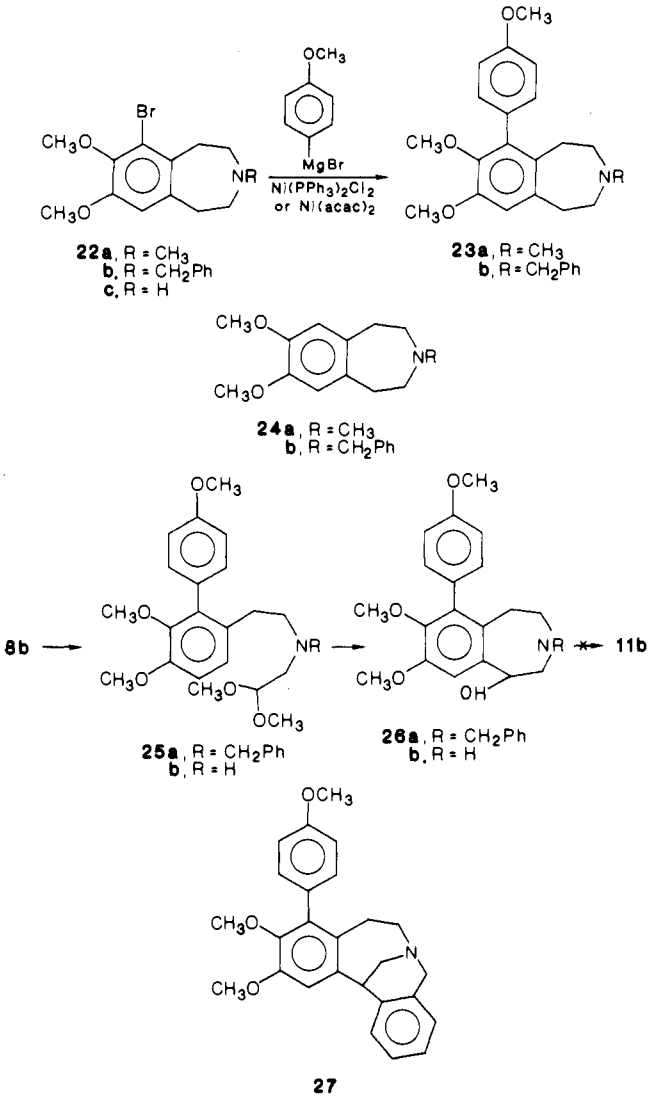
The (aminomethyl)fluorenes (**4a,b**) were prepared from acids **16** as shown in Scheme V. Fluorenones **28** were formed by first converting acids **16** to their acid chlorides under mild conditions followed by reaction of the acid chlorides with stannic chloride. This two-step procedure gave greatly improved yields of the fluorenones (**28**) in comparison to the reported[18] single-step procedure (refluxing thionyl chloride); for example, 94% vs. 30% for **28a**. The fluorenones were catalytically reduced to the fluorenes (**29**), which were converted[24] to the aldehydes (**30**)

(15) Pridgen, L. N. *J. Heterocyclic Chem.* **1980**, *17*, 1289.
(16) Ku, T. W.; McCarthy, M. E.; Bondinell, W. E.; Dandridge, P. A.; Girard, G. R.; Kaiser, C. *J. Org. Chem.* **1982**, *47*, 3862.
(17) Brown, D. W.; Dyke, S. F.; Hardy, G.; Sainsbury, M. *Tetrahedron Lett.* **1968**, 2609.
(18) Burger, A.; Coyne, W. E.; Janssen, G. *J. Med. Chem.* **1963**, *6*, 614.
(19) Flaim, K. E.; Gessner, G. W.; Crooke, S. T.; Sarau, H. M.; Weinstock, J. *Life Sci.* **1985**, *36*, 1427.
(20) TRIPOS Associates, *The SYBYL Molecular Modeling System* Ver. 3.1; TRIPOS Associates: St. Louis, 1984.
(21) This calculated value agrees well with the torsion angle measured by X-ray diffraction, 22.4°, *Acta Crystallogr., Sect. B* **1973**, *29*, 1785.
(22) Allinger, N. L.; Sprague, J. T. *J. Am. Chem. Soc.* **1973**, *95*, 3893.
(23) Sibley, D. R.; DeLean, A.; Creese, I. *J. Biol. Chem.* **1982**, *257*, 6351.

Scheme III



Scheme IV



with ethyl formate and potassium methoxide. Reductive amination of **30** with sodium cyanoborohydride and ammonium acetate gave low yields of **32** with the diamines (**33**) being the major products. Therefore, the oximes (**31**) were formed and catalytically reduced to **32**; reduction over platinum in the presence of chloroform was superior to reduction over Raney nickel, although some over reduction was noted with platinum. The dihydroxy compounds (**4a,b**) were obtained by boron tribromide demethylation.

Discussion

The 2-arylphenethylamines, 6-arylbenzazepines, and 9-(aminomethyl)fluorenes described herein were evaluated for D_1 and D_2 binding activity (Table I). D_1 binding was determined in competition binding studies using tritiated fenoldopam,[19] while D_2 binding was measured in competition studies with tritiated spiroperidol.[23] For comparison purposes binding data for benzazepine **34**, ADTN, apomorphine, fenoldopam, and dopamine are included in the table. As can be seen from the table all of the newly prepared compounds exhibited very weak D_2 binding (IC_{50}'s, and hence K_i's, were obtained only for those compounds that had percent inhibitions at 10^{-5} M of greater than 50%), and only 2-arylphenethylamine (**1d**) was as potent as dopamine. Although more potent binding activity at the D_1 receptor than at the D_2 receptor was detected for the entire group, only the 9-(aminomethyl)-fluorene **4b** showed D_1 binding comparable to apomorphine.

These data show that the introduction of a nonrigid aryl group into the 2-position of dopamine or the equivalent 6-position of a 3-benzazepine leads to compounds with decreased dopamine binding at both D_1 and D_2 receptors. For example, 2-phenyldopamine (**1a**) is about 10-fold less potent than dopamine itself in our D_1 binding assay, which

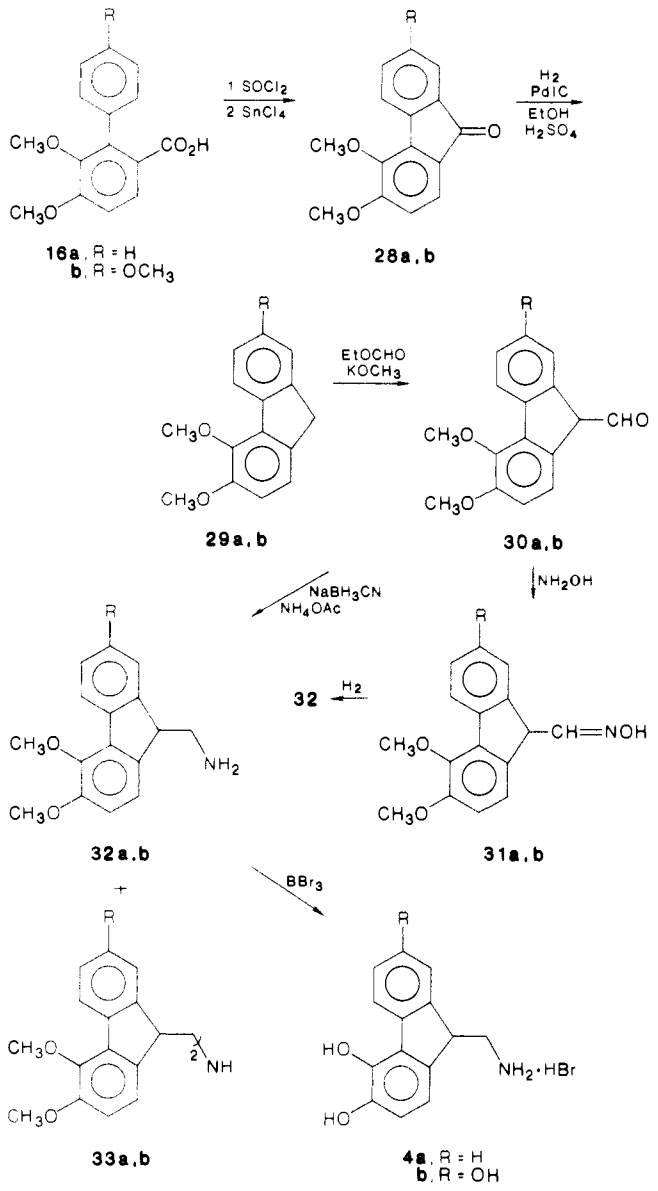
Table I. Binding to Dopamine Receptors[a]

	D_1 ([^{3}H]fenoldopam)		D_2 ([^{3}H]spiroperidol)		
compd	n	K_i, nM	n	% inhibn at 10^{-5} M	K_i, nM
1a	2	1500 (215)	2	IA[b]	
1b	2	1940 (480)	2	29 (10)	
1c	2	1650 (435)	2	IA	
1d	2	1740 (345)	3		1800 [410]
3a	2	1790 (395)	2	IA	
3b	2	700 (235)	2	27 (2)	
3c	2	>3000	2	IA	
3d	2	1630 (305)	3	IA	
4a	2	380 (195)	3	20 [7]	
4b	2	43 (17)	4		5740 [1820]
34	3	970 [280]		ND[c]	
dopamine		150 [25]			2350 [400]
ADTN		57 [9]			255 [45]
apomorphine		53 [12]			200 [10]
fenoldopam		3 [1]			790 [160]

[a] Values were determined in 2–4 separate experiments (n) each testing 2–6 concentrations of the compounds in triplicate. Numbers in parentheses indicate the range above or below the mean. Numbers in brackets indicate the SEM. [b] IA, inactive; defined as <20% inhibition. [c] ND, not determined.

(24) Von, I.; Wagner, E. C. *J. Org. Chem.* **1944**, *9*, 155.

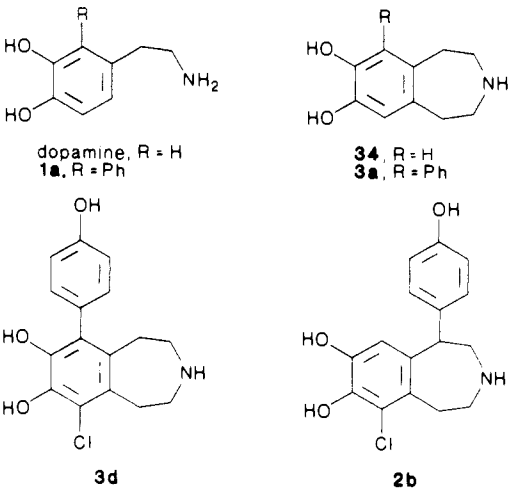
Scheme V



is consistent with Sheppard's[2] finding that **1a** is about 5% as potent as dopamine as a stimulator of dopamine-sensitive adenylate cyclase; 6-phenylbenzazepine (**3a**) is about half as potent as the desphenyl benzazepine **34**, and benzazepine **3d** is more than 100-fold less potent than the isomeric 1-arylbenzazepine fenoldopam (**2b**) in the D_1 binding assay. All of the compounds tested showed weak D_2 binding as measured by displacement of the D_2 antagonist spiroperidol. In contrast to our finding using tritiated spiroperidol as ligand, Seeman[3] found that **1a** has potent D_2 binding activity when measured in competition with D_2 agonists [^{3}H]apomorphine and [^{3}H]dopamine.

The strong D_1 binding observed for apomorphine and for 9-(aminomethyl)fluorene **4b** and to a lesser extent with **4a** argues against the decrease being due to the introduction of hydrophobic bulk at what is the 2-position of dopamine. The data suggest that the rigidity of the apomorphine and fluorene skeletons imparts an orientation to the biphenyl portion of the molecule, which results in enhanced binding to the receptor.

Calculations of the torsion angle between the two aromatic rings of the biphenyl system in SIMPLEX energy-minimized structures[20] support this conclusion. The calculated torsion angles for apomorphine and 9-(aminomethyl)fluorene **4b** are small, 24.3°[21] and 0.0°, respectively.



The calculated torsion angles for 2-phenyldopamine (**1a**) and 6-phenylbenzazepine (**3a**) are 92.6° and 90.0°; thus, the two aromatic rings are orthogonal as expected[22] for a nonrigid, di-*o*-substituted biphenyl. In conclusion, these results indicate that D_1 binding is more favorable in 2-aryldopamine derivatives in which the two aromatic rings of the biphenyl portion of the molecule are nearly coplanar and is less favorable when the aromatic rings are orthogonal.

Experimental Section

Biological Methods. The D_1 binding activity assay was performed by use of homogenized and washed membrane preparations from rat striatum essentially as described previously.[19] Tissues were preincubated for 15 min at 37 °C in 50 mM Tris·HCl, pH 7.4, 10 mM $MgSO_4$, 2 mM EDTA, and 0.1% ascorbate. The binding assay was then carried out in the above buffer also containing 400–500 μg of membrane protein, 10 μM pargyline, 0.1 μM domperidone, [^{3}H]fenoldopam, and test compounds. Incubations proceeded for 45 min at 37 °C. The membrane-bound radioactivity was trapped by rapid filtration over glass fiber (GF/C) filters. In each experiment the amount of [^{3}H]fenoldopam bound was determined in the absence (total) and presence (nonspecific) of 10^{-6} M (+)-butaclamol, the difference yielding specific [^{3}H]fenoldopam binding. The ability of each compound to compete with [^{3}H]fenoldopam (approximately 2.0 nM) was tested at concentrations of 10^{-7} and 10^{-6} M. If a compound was found to displace [^{3}H]fenoldopam by >50% at a concentration of 10^{-6} M, it was considered to have significant activity and was further tested to obtain an IC_{50} for competition against [^{3}H]-fenoldopam. The binding constant of a compound (K_i) was calculated from the equation $K_i = (IC_{50})(1 + (L/K_D))$, where L is the concentration of [^{3}H]fenoldopam and K_D is the equilibrium dissociation constant for fenoldopam (2.0 nM).

The D_2 binding activity assay was performed similarly using homogenized and washed membrane preparations from bovine anterior pituitary essentially as described by Sibley.[23] Binding assays proceeded for 20 min at 37 °C in a 1-mL volume of buffer (50 nM Tris·HCl, pH 7.4, 10 nM $MgSO_4$, 2 mM EDTA, and 0.1% ascorbate) containing 500 μg of membrane protein, 0.2–0.3 nM [^{3}H]spiroperidol, and competing drugs. Specific [^{3}H]spiroperidol binding for each test compound was determined at 10^{-7} and 10^{-5} M. IC_{50}'s were determined for compounds found to displace spiroperidol by >50% at 10^{-5} M. Binding constants were calculated as above using 0.3 nM as the equilibrium dissociation constant for spiroperidol.

Chemistry. All compounds were routinely checked by NMR, TLC, and mass spectroscopy. Proton magnetic spectra were determined on Varian T-60 and EM-390 instruments using Me_4Si as the internal reference. TLC's were run on Uniplate silica gel plates, 250 μm (Analtech, Inc., Newark, DE), using appropriate solvents. Medium-pressure liquid chromatography (MPLC) was carried out on EM silica gel 60 (230–400 mesh) in Altex glass columns using a Fluid Metering, Inc., RRP solvent pump equipped with a PD-60-LF pulse dampener. Mass spectra were obtained

on Hitachi Perkin-Elmer RMN-6E and Varian MAT CH-5 DF spectrometers. Melting points were determined on Laboratory Devices Mel-Temp and Thomas-Hoover Unimelt capillary instruments and are uncorrected. Where elemental analyses are indicated only by symbols of the elements, results were within ±0.4% of the theoretical values.

2-(Chloromethyl)-5,6-dimethoxybiphenyl (6a) from 5. A solution of 20.5 g (0.0958 mol) of 2,3-dimethoxybiphenyl (**5**) in 205 mL of ethylene chloride, 205 mL of concentrated HCl, and 205 mL of 37% CH_2O was refluxed for 6.75 h while HCl gas was continuously bubbled in. The HCl gas was shut off, and reflux was continued for 17 h after which time the mixture was cooled and the layers separated. The aqueous layer was extracted twice with $CHCl_3$ and the extracts combined with the organic layer, which was then washed twice with H_2O, dried over $MgSO_4$, and concentrated. Distillation afforded a 77% yield of colorless liquid: bp 125–135 °C (0.08 mmHg). An analytical sample was prepared by vacuum distillation at 0.5 mmHg: bp 133–135 °C; ^1H NMR ($CDCl_3$) δ 3.53 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 4.31 (s, 2, CH_2Cl), 7.05 (q, 2, ArH), 7.36 (s, 5, ArH). Anal. ($C_{15}H_{15}ClO_2$) C, H.

2-(Cyanomethyl)-5,6-dimethoxybiphenyl (7a). Sodium cyanide, 0.96 g (0.020 mol), was added to a solution of 4.27 g (0.016 mol) of **6a** in 22 mL of Me_2SO. After the reaction mixture was stirred for 1 h at ambient temperature, it was poured into ice water and extracted twice with ether. The combined extracts were washed 4 times with H_2O, dried over $MgSO_4$, and concentrated to 3.87 g (91%) of light yellow oil: ^1H NMR ($CDCl_3$) δ 3.37 (s, 2, CH_2CN), 3.54 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 6.87–7.50 (m, 7, ArH). Anal. ($C_{16}H_{15}NO_2$) C, H, N.

2-(2-Phenyl-3,4-dimethoxyphenyl)ethylamine Hydrochloride (8a·HCl). A solution of 13.04 g (0.0515 mol) of nitrile **7a** in 130 mL of MeOH saturated with NH_3 was hydrogenated on a Parr shaker over Raney nickel catalyst for 3 h at 50 °C and 50 psi. The reaction mixture was then degassed, filtered, and concentrated to 12.77 g (96%) of green oil (**8**): ^1H NMR ($CDCl_3$) δ 1.07 (br s, 2, NH_2), 2.53 (m, 4, CH_2CH_2), 3.50 (s, 3, OCH_3), 3.85 (s, 3, OCH_3), 6.88 (q, 2, ArH), 7.25 (m, 5, ArH).

The hydrochloride salt (**8a**·HCl) was prepared by treating an ether solution of **8a** with ethereal HCl followed by recrystallization from MeOH/EtOAc/hexane: mp 215–216.5 °C. Anal. ($C_{16}H_{20}ClNO_2$) C, H, N.

2-(2-Phenyl-3,4-dihydroxyphenyl)ethylamine Hydrobromide (1a·HBr). A 1.0 M solution of BBr_3 in CH_2Cl_2 (40.8 mL, 0.0408 mol) was added dropwise with ice-bath cooling to a solution of 3.50 g (0.0136 mol) of **8a** in 100 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 1.5 h, then excess MeOH was added slowly with cooling. The resultant solution was concentrated to a foamy oil, which yielded 2.57 g (61%) of hydroscopic white crystalline solid from MeOH/EtOAc: mp 196 °C (softening at 130 °C); ^1H NMR (Me_2SO-d_6) δ 2.67 (br s, 4, CH_2CH_2), 6.70 (q, 2, ArH), 7.02–7.55 (m, 5, ArH), 7.82 (br s, D_2O exchangeable). Anal. ($C_{14}H_{16}BrNO_2$·0.5H_2O) C, H, N.

2,3-Bis(cyanomethyl)-5,6-dimethoxybiphenyl (10). A solution of 30.1 g (0.140 mol) of 2,3-dimethoxybiphenyl, 300 mL of dioxane, and 30 mL of 37% CH_2O was heated at 90 °C and HCl gas was bubbled in for 6 h. An additional 95 mL of 37% CH_2O, 200 mL of dioxane, and 90 g of paraformaldehyde were added in portions during the course of the reaction. The HCl gas was turned off, and the reaction mixture was left overnight at room temperature. The mixture was poured into ice water and extracted 3 times with $CHCl_3$. Then the combined extracts were washed 4 times with H_2O, dried over $MgSO_4$, and concentrated to 56.7 g of dark oil. The oil was dissolved in 500 mL of benzene and shaken with 300 mL of concentrated HCl. The benzene layer was washed twice with H_2O, dried over $MgSO_4$, and concentrated to 46.5 g of crude **9** as a viscous tan oil. Sodium cyanide, 17.2 g (0.350 mol), was added to a solution of 45.6 g (0.149 mol) of crude **9** in 600 mL of Me_2SO with cooling during which the temperature rose to 46 °C. After the reaction mixture was stirred for 1 h at ambient temperature, it was poured into ice water and extracted 4 times with $CHCl_3$. The combined extracts were washed 4 times with H_2O, dried over $MgSO_4$, and concentrated to 43.7 g of crude **10** as a dark oil. An analytical sample was obtained by chromatography on silica gel eluting with $CHCl_3$ with a MeOH gradient: mp 124–128 °C; ^1H NMR ($CDCl_3$) δ 3.35 (s, 2, CH_2CN), 3.52 (s, 3, OCH_3), 3.82 (s, 2, CH_2CN), 3.92 (s, 3, OCH_3), 6.97–7.53 (m, 6, ArH). Anal. ($C_{18}H_{16}N_2O_2$·0.25H_2O) C, H, N.

2,3,4,5-Tetrahydro-7,8-dimethoxy-6-phenyl-1*H*-3-benzazepine (11a) from 10. A solution of 33.0 g (0.113 mol) of **10** in 750 mL of ammonia-saturated EtOH was hydrogenated over 7.5 g of Raney nickel catalyst for 5 h at 100 °C with an initial pressure of 1000 psi. The mixture was cooled, filtered, and concentrated. The residue was dissolved in $CHCl_3$, and 80 mL of trifluoroacetic anhydride was added with cooling. After stirring for 4 h at room temperature, the solution was concentrated to 55.9 g of dark oil, which was chromatographed on 1200 g of silica gel ($CHCl_3$ with a 0–5% MeOH gradient) giving 15.72 g of partially purified trifluoroacetamide. This material was rechromatographed on silica gel ($CHCl_3$): 1.42 g of pure trifluoroacetamide was obtained as a yellow solid. A slurry of 1.32 g (3.48 mmol) of trifluoroacetamide, two pellets of KOH, and 25 mL of MeOH was stirred at room temperature for 1.5 h. The resultant solution was diluted with H_2O and extracted several times with Et_2O. The combined extracts were washed with H_2O, dried over $MgSO_4$, and concentrated to 0.93 g of crude **11**. Chromatography on 15 g of silica gel ($CHCl_3$ with a 0–20% MeOH gradient) yielded 0.72 g (2.2%) of pure **11** as an oil: ^1H NMR ($CDCl_3$) δ 2.51–3.11 (m, 9, CH_2's and NH), 3.49 (s, 3, OCH_3), 3.87 (s, 3, OCH_3), 6.71 (s, 1, ArH, 9-position), 6.37–7.48 (m, 5, Ph).

2,3,4,5-Tetrahydro-6-phenyl-1*H*-3-benzazepine-7,8-diol Hydrobromide (3a·HBr). Treatment of 0.72 g (2.54 mmol) of **11a** with 10.2 mmol of BBr_3 for 5 h as described for **1a** afforded 0.86 g (100%) of **3a**·HBr: mp 316–320 °C dec; ^1H NMR (Me_2SO-d_6) δ 6.70 (s, 1, ArH, 9-position). Anal. ($C_{16}H_{18}BrNO_2$·0.25H_2O) C, H, N.

2-(2,3,4-Trimethoxyphenyl)-4,4-dimethyl-2-oxazoline (13). Thionyl chloride (5.16 mL, 0.0707 mol) was added to 5.00 g (0.0236 mol) of **12** and the resultant mixture stirred overnight at room temperature under N_2. The mixture was concentrated on a rotary evaporator and the residue dissolved in toluene and concentrated again. A solution of the acid chloride in 10 mL of CH_2Cl_2 was added slowly at 0 °C to a solution of 2-amino-2-methyl-1-propanol (4.50 mL, 0.0472 mol) in 10 mL of CH_2Cl_2. The resultant suspension was stirred at room temperature for 3 h and filtered. The filtrate was washed twice with H_2O, dried over $MgSO_4$, and concentrated to yield 5.80 g (87%) of benzamide as a white solid: mp 100–103 °C. Thionyl chloride (4.70 mL, 0.0644 mol) was added dropwise to the benzamide (5.60 g, 0.0198 mol) causing a vigorous exothermic reaction resulting in a yellow solution, which was stirred at room temperature for a few minutes. Addition of ether produced a yellow oil. The ether was decanted and fresh ether added, causing the oil to crystallize. The hydroscopic crystals were filtered, washed with ether, and dissolved in H_2O. Neutralization with 40% NaOH with cooling followed by ether extraction, drying over $MgSO_4$, and concentration produced 4.67 g (89%) of yellow liquid, which slowly crystallized: mp 43–46 °C [lit.[13] mp 43–44 °C].

2-(2-Phenyl-3,4-dimethoxyphenyl)-4,4-dimethyl-2-oxazoline (14a). A solution of 5.31 g (0.020 mol) of **13** in 28 mL of THF was added slowly to 35.3 mL (0.060 mol) of 1.7 M ethereal phenylmagnesium bromide causing a mild exothermic reaction. The resultant brown solution was stirred overnight at room temperature then quenched with saturated NH_4Cl solution with cooling. The aqueous phase was extraced with THF; the extract was combined with the THF layer and then washed with saturated NaCl solution and concentrated. The residue was dissolved in 10% HCl, washed twice with ether, and then made basic with cold 50% NaOH and extracted twice with EtOAc. The EtOAc extracts were washed with H_2O, dried over $MgSO_4$, and concentrated to 5.09 g (82%) of **14a** as an oil, which crystallized on standing: mp 100–103 °C; ^1H NMR ($CDCl_3$) δ 1.18 (s, 6, CH_3), 3.51 (s, 3, OCH_3), 3.63 (s, 2, CH_2), 3.90 (s, 3, OCH_3), 7.17 (q, 2, ArH), 7.33 (s, 5, Ph). Anal. ($C_{19}H_{21}NO_3$) C, H, N.

2-[2-(4-Methoxyphenyl)-3,4-dimethoxyphenyl]-4,4-dimethyl-2-oxazoline (14b). Compound **13** (3.87 g, 0.0146 mol) treated with 0.0423 mol of *p*-methoxyphenylmagnesium bromide as described for **14a** yielded 4.04 g (81%) of compound **14b**: mp 118–123 °C; ^1H NMR ($CDCl_3$) δ 1.20 (s, 6, CH_3), 3.49 (s, 3, OCH_3), 3.68 (s, 2, CH_2), 3.82 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 6.80–7.43 (m, 6, ArH). Anal. ($C_{20}H_{23}NO_4$) C, H, N.

2-(2-Phenyl-3,4-dimethoxyphenyl)-3,4,4-trimethyloxazolinium Iodide (15a). Iodomethane (4.59 mL, 0.0737 mol)

was added dropwise to a solution of 4.59 g (0.0147 mol) of **14a** in 46 mL of nitromethane, and the solution was stirred overnight at room temperature after which time some solids were present. The mixture was diluted with 135 mL of ether, and the precipitated product was filtered and washed with ether to yield 6.71 g (100%) of **15a**: mp 184–186 °C dec. An analytical sample was prepared by recrystallization from EtOH/EtOAc/hexane: mp 187–188.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 6, CCH_3), 2.78 (s, 3, NCH_3), 3.54 (s, 3, OCH_3), 3.97 (s, 3, OCH_3), 4.97 (s, 2, CH_2), 7.10–7.57 (m, 6, ArH), 8.22 (d, 1, ArH). Anal. ($C_{20}H_{24}INO_3$) C, H, N.

2-[2-(4-Methoxyphenyl)-3,4-dimethoxyphenyl]-3,4,4-trimethyloxazolinium Iodide (15b). Compound **15b** was prepared in 94% yield from **14b** and iodomethane as described for **15a**: mp 228.5–232.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.51 (s, 6, CCH_3), 2.79 (s, 3, NCH_3), 3.57 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 4.00 (s, 3, OCH_3), 5.04 (s, 2, CH_2), 6.96–7.30 (m, 5, Ar), 8.22 (d, 1, ArH). Anal. ($C_{21}H_{26}INO_4$) C, H, N.

3,4-Dimethoxy-2-phenylbenzoic Acid (16a). A mixture of 43.27 g (0.0955 mol) of **15a**, 433 mL of MeOH, and 433 mL of 20% NaOH was refluxed overnight, then concentrated until cloudy. Sufficient water was added to give a solution, which was washed with ether and acidified with concentrated HCl with cooling. The precipitated product was filtered, washed with H_2O, and dried to yield 21.71 g (88%): mp 194.5–196.5 °C. An analytical sample was prepared by recrystallization from toluene: mp 195–197.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.46 (s, 3, OCH_3), 3.91 (s, 3, OCH_3), 7.09–7.67 (m, 7, ArH), 12.20 (br s, 1, CO_2H). Anal. ($C_{15}H_{14}O_4 \cdot 0.25H_2O$) C, H.

3,4-Dimethoxy-2-(4-methoxyphenyl)benzoic Acid (16b). Compound **16b** was prepared in 98% yield from **15b** as described for **16a**: mp 213.5–214.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.46 (s, 3, OCH_3), 3.81 (s, 3, OCH_3), 3.90 (s, 3, OCH_3), 7.03 (q, 4, ArH), 7.33 (q, 2, ArH). Anal. ($C_{16}H_{16}O_5$) C, H.

5,6-Dimethoxy-2-biphenylmethanol (17a). A 0.98 M solution of BH_3 in THF (122.4 mL, 0.120 mol) was added dropwise to a suspension of **16a**, 25.83 g (0.100 mol), at room temperature under nitrogen. After stirring overnight, MeOH was added dropwise with cooling. A small amount of insoluble material was removed by filtration and the filtrate concentrated to an oil. The oil was redissolved in MeOH, concentrated, and dissolved in CH_2Cl_2. The CH_2Cl_2 solution was washed with 5% $NaHCO_3$, dried over $MgSO_4$, and concentrated to 23.76 g (97%) of product as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.03 (br s, 1, OH), 3.52 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 4.30 (br s, 2, CH_2), 7.03 (q, 2, ArH), 7.33 (m, 5, Ph). Anal. ($C_{15}H_{16}O_3 \cdot 0.25H_2O$) C, H.

4',5,6-Trimethoxy-2-biphenylmethanol (17b). Acid **16b**, 16.0 g (0.0555 mol), was added in portions under nitrogen to a suspension of 4.17 g (0.110 mol) of lithium aluminum hydride in 320 mL of THF. The mixture was refluxed for 4 h, then cooled in an ice bath and 4.17 mL of H_2O, 6.26 mL of 10% NaOH, and 10.43 mL of H_2O added successively in a dropwise manner producing a white suspension. The suspension was filtered and the precipitate washed with THF. The THF filtrate and washing were combined and concentrated to give 14.39 g (95%) of an oil, which crystallized to a white solid: mp 94.5–97 °C; ^{1}H NMR ($CDCl_3$) δ 1.86 (br s, 1, OH), 3.52 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 4.34 (br s, 2, CH_2), 6.84–7.24 (m, 6, ArH). Anal. ($C_{16}H_{18}O_4$) C, H.

2-(Chloromethyl)-5,6-dimethoxybiphenyl (6a) from 17a. Concentrated HCl (40 mL) was added to a solution of **17a**, 14.23 g (0.0583 mol), in 80 mL of toluene and heated and stirred on a steam bath for 1 h. The reaction mixture was cooled, and the layers were separated. The organic layer was washed twice with H_2O, dried over $MgSO_4$, and concentrated to 14.45 g (94%) of light yellow oil identical in all respects to **6a** produced by chloromethylation of **5**.

2-(Chloromethyl)-4',5,6-trimethoxybiphenyl (6b). Compound **6b** was prepared in 92% yield from **17b** as described for **6a**: ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 3, OCH_3), 3.81 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 4.30 (s, 2, CH_2Cl), 6.80–7.24 (m, 6, ArH). Anal. ($C_{16}H_{17}ClO_3$) C, H, Cl.

2-(Cyanomethyl)-4',5,6-trimethoxybiphenyl (7b). Compound **7b** was prepared in 95% yield from **6b** as described for **7a**: mp 79.5–82.5 °C (subsequent preparations gave apparently polymorphous material of mp 102–104 °C with identical ^{1}H NMR and IR spectra); ^{1}H NMR ($CDCl_3$) δ 3.38 (s, 2, CH_2CN), 3.52 (s, 3, OCH_3), 3.83 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 6.87–7.24 (m, 6, ArH). Anal. ($C_{17}H_{17}NO_3$) C, H, N.

2-[2-(4-Methoxyphenyl)-3,4-dimethoxyphenyl]ethylamine Hydrochloride (8b·HCl). The free base (**8b**) was obtained as a green oil in 98% yield from **7b** as described for **8a**: ^{1}H NMR ($CDCl_3$) δ 1.03 (br s, 2, NH_2), 2.60 (octet, 4, CH_2CH_2), 3.54 (s, 3, OCH_3), 3.87 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 6.84–7.24 (m, 6, ArH).

The hydrochloride salt (**8b·HCl**) was prepared as described for **8a·HCl**: mp 175.5–177.5 °C (EtOH/ether). Anal. ($C_{17}H_{22}ClNO_3$) C, H, N.

***N*,*N*-Di-*n*-propyl-2-(2-phenyl-3,4-dimethoxyphenyl)ethylamine *d*-Tartrate (18a·*d*-$C_4H_6O_6$).** A solution of **8a** (3.91 g, 0.0152 mol) and propionaldehyde (3.29 mL, 0.0456 mol) in 78 mL of glacial acetic acid was hydrogenated at 60 psi over 0.39 g of 10% palladium on charcoal on a Parr shaker for 3 h at room temperature. The filtered mixture was concentrated to an oil, which was dissolved in H_2O and washed with Et_2O. The aqueous solution was then made basic with 50% NaOH and extracted twice with ether. The combined extracts were dried over $MgSO_4$ and concentrated to 3.22 g (62%) of free base as an oil: ^{1}H NMR ($CDCl_3$) δ 0.76 (t, 6, CH_2CH_3), 1.23 (sextet, 4, $CH_2CH_2CH_3$), 2.20 (t, 4, $CH_2CH_2CH_3$), 2.47 (br s, 4, $ArCH_2CH_2N$), 3.53 (s, 3, OCH_3), 3.87 (s, 3, OCH_3), 6.91 (q, 2, ArH), 7.31 (m, 5, Ph).

The *d*-tartaric acid salt was prepared by adding an ethanol solution of *d*-tartaric acid (0.59 g, 3.93 mmol) to an ether solution of **18a** (1.22 g, 3.57 mmol). Dilution with hexane produced an oil, which was triturated successively with ether and hexane to produce 0.80 g (44%) of amorphous white solid. Anal. ($C_{26}H_{37}NO_8 \cdot H_2O$) C, H, N.

***N*,*N*-Di-*n*-propyl-2-[2-(4-methoxyphenyl)-3,4-dimethoxyphenyl]ethylamine *d*-Tartrate (18b·*d*-$C_4H_6O_6$).** Compound **8b**·*d*-$C_4H_6O_6$ was prepared in 79% yield as an oil from **8b** as described for **18a**: ^{1}H NMR ($CDCl_3$) δ 0.74 (t, 6, CH_2CH_3), 1.23 (sextet, 4, $CH_2CH_2CH_3$), 2.20 (t, 4, $CH_2CH_2CH_3$), 2.46 (br s, 4, $ArCH_2CH_2N$), 3.53 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 6.92 (q, 2, ArH), 7.04 (q, 4, ArH).

The *d*-tartaric acid salt was prepared in 87% yield from **18b** as described for **18a**: mp 107.5–113.5 °C. Anal. ($C_{27}H_{39}NO_9 \cdot 0.5H_2O$) C, H, N.

2-[2-(4-Hydroxyphenyl)-3,4-dihydroxyphenyl]ethylamine Hydrobromide (1c·HBr). Treatment of 2.49 g (8.67 mmol) of **8b** with 43.3 mmol of BBr_3 for 23 h as described for **1a** afforded 0.81 g (29%) of product: mp 207.5–208.5 °C; ^{1}H NMR (Me_2SO-d_6) δ 2.61 (m, 4, $CH_2CH_2NH_2$), 6.44–6.99 (m, 6, ArH). Anal. ($C_{14}H_{16}BrNO_3$) C, H, N.

***N*,*N*-Di-*n*-propyl-2-(2-phenyl-3,4-dihydroxyphenyl)ethylamine Hydrobromide (1b·HBr).** Overnight reaction of **18a** (1.96 g, 5.74 mmol) with 4 mol of BBr_3 as described for **1a** yielded 1.82 g (81%) of product: mp 195–197.5 °C (MeOH/EtOAc); ^{1}H NMR (Me_2SO-d_6) δ 0.77 (t, 6, CH_2CH_3), 1.32 (m, 4, $CH_2CH_2CH_3$), 2.74 (m, 8, $ArCH_2CH_2N$ and $NCH_2CH_2CH_3$), 6.76 (q, 2, ArH), 7.32 (m, 5, Ph). Anal. ($C_{20}H_{28}BrNO_2 \cdot 0.25H_2O$) C, H, N.

***N*,*N*-Di-*n*-propyl-2-[2-(4-hydroxyphenyl)-3,4-dihydroxyphenyl]ethylamine Hydrobromide (1d·HBr).** Overnight reaction of **18b** (2.47 g, 6.65 mmol) with 33.3 mmol of BBr_3 as described for **1a** followed by purification of the crude product by MPLC on silica gel eluting with CH_2Cl_2 containing 5% MeOH gave 0.90 g (33%) of white amorphous solid: ^{1}H NMR ($CDCl_3$/Me_2SO-d_6) δ 0.88 (t, 6, CH_2CH_3), 1.52 (m, 4, $CH_2CH_2CH_3$), 2.62–2.87 (m, 8, $ArCH_2CH_2N$ and $NCH_2CH_2CH_3$), 6.78 (q, 2, ArH), 7.04 (q, 4, ArH). Anal. ($C_{20}H_{28}BrNO_3$) C, H, N.

***N*-[2-(2-Phenyl-3,4-dimethoxyphenyl)ethyl]chloroacetamide (19a).** Amine **8a** (10.40 g, 0.0404 mol) and chloroacetyl chloride (4.83 mL, 0.0606 mol) were each dissolved in 81 mL of toluene and added simultaneously over a 10-min period with cooling at 10–15 °C to 81 mL of 1.0 N NaOH. The cooling bath was removed and stirring continued for 15 min, then the layers were separated. The aqueous layer was extracted with toluene and the extract combined with the toluene layer. The combined toluene solutions were then washed with 10% HCl, dried over $MgSO_4$, and concentrated to 12.44 g (92%) of oil, which slowly crystallized: mp 97–99.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.58 (t, 2, CH_2CH_2N), 3.26 (q, 2, CH_2CH_2N), 3.51 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 3.92 (s, 2, CH_2Cl), 6.40 (m, 1, NH), 6.92 (q, 2, ArH),

7.22–7.42 (m, 5, Ph). Anal. ($C_{18}H_{20}ClNO_3$) C, H, N.

***N*-[2-[2-(4-Methoxyphenyl)-3,4-dimethoxyphenyl]ethyl]-chloroacetamide (19b).** Amine **8b** (7.16 g, 0.0249 mol) and chloroacetyl chloride (2.99 mL, 0.0375 mol) were reacted with 50 mL of 1.0 N NaOH as described for **19a**. Some of the product precipitated during the reaction and was isolated by filtration giving 2.73 g: mp 120–122 °C. The filtrate was worked up as described giving an additional 5.22 g: mp 120–122 °C (total yield, 88%); ^{1}H NMR ($CDCl_3$) δ 2.63 (t, 2, CH_2CH_2N), 3.29 (q, 2, CH_2CH_2N), 3.52 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 3.94 (s, 2, CH_2Cl), 6.39 (br s, 1, NH), 6.81–7.26 (m, 6, ArH). Anal. ($C_{19}H_{22}ClNO_4$) C, H, N.

1,2,4,5-Tetrahydro-7,8-dimethoxy-6-phenyl-3*H*-3-benzazepin-2-one (21a). A solution of **19a** (3.48 g, 0.0104 mol) in 1400 mL of 50% aqueous EtOH was irradiated in a quartz apparatus under argon with a 200-W mercury lamp for 27 h. The solution was made neutral with 10% NaOH, then concentrated until cloudy and extracted twice with EtOAc. The combined extracts were dried over $MgSO_4$ and concentrated to 2.83 g of crude product, which was purified by MPLC on silica gel eluting with EtOAc. The components eluted in the following order: **19a**, **20a**, **21a**; 1.33 g (43%) of purified **21a** was obtained: mp 168–169.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.68 (t, 2, CH_2CH_2N), 3.36 (t, 2, CH_2CH_2N), 3.51 (s, 3, OCH_3), 3.82 (s, 2, $CH_2C{=}O$), 3.88 (s, 3, OCH_3), 6.42 (m, 1, NH), 6.76 (s, 1, ArH), 7.11–7.48 (m, 5, Ph). Anal. ($C_{18}H_{19}NO_3$) C, H, N.

1,2,4,5-Tetrahydro-7,8-dimethoxy-6-(4-methoxyphenyl)-3*H*-3-benzazepin-2-one (21b). A solution of **19b** (3.64 g, 0.010 mol) in 1400 mL of 50% aqueous EtOH was irradiated with a 450-W mercury lamp for 22 h and worked up as described for **21a** to give 1.08 g (33%) of product: mp 170.5–174 °C; ^{1}H NMR ($CDCl_3$) δ 2.71 (t, 2, CH_2CH_2N), 3.36 (dd, 2, CH_2CH_2N), 3.51 (s, 3, OCH_3), 3.82 (s, 2, $CH_2C{=}O$), 3.86 (s, 3, OCH_3), 3.88 (s, 3, OCH_3), 6.29 (br s, 1, NH), 6.74 (s, 1, ArH), 7.02 (q, 4, ArH). Anal. ($C_{19}H_{21}NO_4$) C, H, N.

2,3,4,5-Tetrahydro-7,8-dimethoxy-6-phenyl-1*H*-3-benzazepine Hydrochloride (11a·HCl) from 21a. A 1.0 M solution of BH_3 in THF (42.1 mL, 0.0421 mol) was added dropwise with ice-bath cooling under a N_2 atmosphere to a solution of 4.17 g (0.0140 mol) of lactam **21a** in 84 mL of THF. The resultant solution was refluxed for 2 h, then cooled in an ice bath, and 42.1 mL of 1.0 N HCl was added dropwise. The solution was brought to reflux and some of the THF removed by distillation. Sufficient water was then added to the reaction mixture to make it cloudy. After the mixture cooled, it was made basic with 10% NaOH and extracted 3 times with Et_2O. The combined extracts were washed once with 10% NaOH and once with H_2O, dried over $MgSO_4$, and concentrated to 3.54 g (89%) of free base **11a** as a foamy oil.

The hydrochloride (**11a**·HCl) was prepared by treating an ether solution of **11a** (0.61 g, 2.2 mmol) with ethereal HCl to give 0.58 g (84%) of white crystalline solid: mp 259 °C dec. Anal. ($C_{18}H_{22}ClNO_2$) C, H, N.

2,3,4,5-Tetrahydro-7,8-dimethoxy-6-(4-methoxyphenyl)-1*H*-3-benzazepine Hydrochloride (11b·HCl). The free base (**11b**) was prepared in 89% yield from **21b** as described for **11a**: ^{1}H NMR ($CDCl_3$) δ 1.97 (br s, 1, NH), 2.49–3.03 (m, 8, CH_2), 3.49 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 6.71 (s, 1, ArH), 7.02 (q, 4, ArH).

The hydrochloride (**11b**·HCl) was prepared from **11b** as previously described for **11a**: mp 219–222 °C dec. Anal. ($C_{19}H_{24}ClNO_3$) C, H, N.

2,3,4,5-Tetrahydro-6-(4-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol Hydrobromide (3c·HBr). Treatment of 1.05 g (3.35 mmol) of **11b** with 16.75 mmol of BBr_3 for 18 h as described for **1a** afforded 0.83 g (70%) of **3c**·HBr: mp 273 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 6.67 (s, 1, ArH), 6.86 (q, 4, ArH). Anal. ($C_{16}H_{18}BrNO_3$) C, H, N.

6-Chloro-2,3,4,5-tetrahydro-9-phenyl-1*H*-3-benzazepine-7,8-diol Hydrochloride (3b·HCl). A warm solution of 3.41 g (10.1 mmol) of **3a**·HBr in 100 mL of MeOH was added slowly with cooling to 200 mL of 5% $NaHCO_3$. The free base (**3a**) that precipitated was collected by filtration, washed with H_2O, and suspended in 89 mL of 9 N HCl. Slow addition of a solution of 2.53 g (11.1 mmol) of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 194 mL of CH_3CN to this suspension gave a dark-red solution, which was stirred overnight at room temperature. Excess solid sodium bisulfite was then added to the solution, which was stirred for 20 min and filtered. The filtrate was concentrated until a precipitate formed. The precipitate was removed by filtration and the cooled filtrate diluted with H_2O to give 1.03 g of crude product, which was recrystallized from MeOH/EtOAc affording 0.42 g (13%) of **3b**·HCl: mp 291 °C dec. Anal. ($C_{16}H_{17}Cl_2NO_2$) C, H, N.

6-Chloro-2,3,4,5-tetrahydro-9-(4-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol Hydrochloride (3d·HCl). Compound **3d**·HCl was prepared in 28% yield from **3c**·HBr as described for **3b**: mp 319 °C dec. Anal. ($C_{16}H_{17}Cl_2NO_3$) C, H, N.

[*N*-Benzyl-*N*-[2-[2-(4-methoxyphenyl)-3,4-dimethoxyphenyl]ethyl]amino]acetaldehyde Dimethyl Acetal (25a). A solution of 5.37 g (0.0187 mol) of amine **8b** and 2.18 g (0.0206 mol) of benzaldehyde in 20 mL of EtOH was stirred at ambient temperature for 15 min. Then a cold solution of 1.87 g (0.0347 mol) of KBH_4 in 10 mL of H_2O was added with cooling. The mixture was stirred at room temperature for 3 h, then acidified with 6 N HCl with cooling and diluted with H_2O. The product was extracted twice with CH_2Cl_2, and the dried (Na_2SO_4) extracts were concentrated to 7.82 g of oily hydrochloride salt. The free base was formed by adding dilute NaOH to 7.50 g of the HCl salt and extracting twice with ether. The extracts were dried over Na_2SO_4 and concentrated to 6.62 g (98%) of *N*-benzyl-**8b** as an oil: ^{1}H NMR ($CDCl_3$) δ 1.33 (br s, 1, NH), 2.59 (s, 4, $ArCH_2CH_2N$), 3.50 (s, 3, OCH_3), 3.63 (s, 2, CH_2Ph), 3.81 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 6.77–7.37 (m, 11, ArH). A solution of 3.56 g (0.0210 mol) of bromoacetaldehyde dimethyl acetal in 22 mL of DMF was added to a mixture of 6.62 g (0.0175 mol) of *N*-benzyl-**8b**, anhydrous K_2CO_3 (5.80 g, 0.0420 mol), and 44 mL of DMF, then refluxed overnight under an atmosphere of N_2. The cooled mixture was filtered and concentrated to a dark oil, which was treated with H_2O and extracted 3 times with EtOAc. The combined extracts were washed with saturated NaCl, then dried over Na_2SO_4 and concentrated to 7.45 g (91%) of crude product. Purified **25a** was obtained as a viscous yellow oil by MPLC on silica gel eluting with CH_2Cl_2 with an EtOAc gradient (0–5%): ^{1}H NMR ($CDCl_3$) δ 2.47 (d, 2, NCH_2CH), 2.52 (s, 4, $ArCH_2CH_2N$), 3.24 (s, 6, $CH(OCH_3)_2$), 3.49 (s, 5, OCH_3 and CH_2Ph), 3.83 (s, 3, OCH_3), 3.86 (s, 3, OCH_3), 4.23 (t, 1, $CH(OCH_3)_2$), 6.71–7.38 (m, 11, ArH). Anal. ($C_{28}H_{35}NO_5$) C, H, N.

2,3,4,5-Tetrahydro-1-hydroxy-7,8-dimethoxy-6-(4-methoxyphenyl)-1*H*-3-benzazepine Hydrochloride (26b·HCl). A mixture of 10.30 g (0.0221 mol) of crude **25a**, 200 mL of EtOH, and 1.0 g of 10% palladium on charcoal was hydrogenated on a Parr shaker for 5 h at 65 °C. The cooled mixture was filtered and concentrated to 8.05 g of crude product, which was purified by MPLC on silica gel eluting with CH_2Cl_2 with a MeOH gradient (0–5%); 2.96 g (36%) of purified **25b** was obtained as an amber oil: ^{1}H NMR ($CDCl_3$) δ 1.31 (br s, 1, NH), 2.57 (m, 6, NCH_2CH and $ArCH_2CH_2N$), 3.32 (s, 6, $CH(OCH_3)_2$), 3.50 (s, 3, OCH_3), 3.84 (s, 3, OCH_3), 3.87 (s, 3, OCH_3), 4.34 (t, 1, $CH(OCH_3)_2$), 6.80–7.26 (m, 6, ArH). Cold 18 N H_2SO_4 (102 mL) was added to 2.54 g (6.77 mmol) of **25b** and the resultant solution stirred overnight at room temperature, then filtered and poured onto ice. Some gummy tan precipitate was removed by filtration. The filtrate was then made basic with 50% NaOH with cooling and extracted twice with EtOAc. The combined extracts were washed with H_2O, dried over $MgSO_4$, and concentrated to 1.55 g (70%) of crude **26b**: mp 185–197 °C. Purified **26b** was obtained by MPLC on silica gel eluting with CH_2Cl_2 with a MeOH gradient (10–20%): mp 208–209 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.38 (s, 3, OCH_3), 3.78 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 4.68 (br d, 1, $ArCH(OH)$), 6.97 (s, 4, ArH), 7.13 (s, 1, ArH). Anal. ($C_{19}H_{23}NO_4$) C, H, N.

The hydrochloride (**26b**·HCl) was prepared by treating an EtOH slurry of **26b** with ethereal HCl, then adding Et_2O/hexane to precipitate the product: mp 233 °C dec. Anal. ($C_{19}H_{24}ClNO_4$) C, H, N, Cl.

3,4-Dimethoxyfluorenone (28a). Thionyl chloride (9.78 mL, 0.134 mol) was added to a suspension of 23.08 g (0.0894 mol) of acid **16a** in 460 mL of CH_2Cl_2, then refluxed for 1.5 h under an atmosphere of N_2. The resultant solution was cooled in an ice bath and 13.07 mL (0.112 mol) of $SnCl_4$ added. After stirring for 2 h at 0 °C, the dark mixture was poured into ice water. The layers were separated, and the aqueous layer was extracted twice with CH_2Cl_2. The combined CH_2Cl_2 solutions were washed twice with

5% $NaHCO_3$, dried over $MgSO_4$, and concentrated to give 20.25 g (94%) of yellow solid: mp 143–144.5 °C [lit.[18] mp 145.5 °C]; ^1H NMR ($CDCl_3$) δ 3.94 (s, 3, OCH_3), 3.98 (s, 3, OCH_3), 6.72 (d, 1, ArH), 7.17–7.89 (m, 5, ArH).

2,5,6-Trimethoxyfluorenone (28b). Compound **28b** was prepared as a yellow solid in 99% yield from acid **16b** as described for **28a**: mp 130.5–132 °C; ^1H NMR ($CDCl_3$) δ 3.83 (s, 3, OCH_3), 3.91 (s, 3, OCH_3), 3.92 (s, 3, OCH_3), 6.61 (d, 1, ArH), 6.92 (dd, 1, ArH), 7.14 (d, 1, ArH), 7.33 (d, 1, ArH), 7.68 (d, 1, ArH). Anal. ($C_{16}H_{14}O_4$) C, H.

3,4-Dimethoxyfluorene (29a). A mixture of 5.73 g (0.0238 mol) of **28a**, 200 mL of EtOH, 0.57 g of 10% palladium on charcoal, and 5 drops of concentrated H_2SO_4 was hydrogenated on a Parr shaker at 50 psi and 60 °C for 3 h, then for 1 h at room temperature. The filtered mixture was concentrated and the residue dissolved in Et_2O. The ether solution was washed twice with 5% $NaHCO_3$, dried over $MgSO_4$, and concentrated to give 4.93 g (91%) of pure product as an oil, which crystallized on standing: mp 62–63.5 °C; ^1H NMR ($CDCl_3$) δ 3.77 (s, 2, CH_2), 3.83 (s, 3, OCH_3), 3.97 (s, 3, OCH_3), 6.76 (d, 2, ArH), 7.03–7.47 (m, 4, ArH), 8.11 (m, 1, ArH). Anal. ($C_{15}H_{14}O_2$) C, H.

2,5,6-Trimethoxyfluorene (29b). Ketone **28b** (11.59 g, 0.0429 mol) was divided into two portions, and each portion was hydrogenated for 6 h at 60 °C with 200 mL of EtOH, 1.5 g of 10% palladium on charcoal, and 1.0 mL of concentrated H_2SO_4. The two reaction mixtures were worked up together as described for **29a** to yield 9.18 g (84%) of product: mp 87–91 °C; ^1H NMR ($CDCl_3$) δ 3.77 (s, 2, CH_2), 3.81 (s, 3, OCH_3), 3.87 (s, 3, OCH_3), 3.97 (s, 3, OCH_3), 6.73 (d, 1, ArH), 6.82–7.18 (m, 3, ArH), 7.99 (d, 1, ArH). Anal. ($C_{16}H_{16}O_3$) C, H.

3,4-Dimethoxyfluorene-9-carboxaldehyde (30a). Ethyl formate (3.82 mL, 0.0437 mol) and $KOCH_3$ (4.15 g, 0.0591 mol) were added to a solution of 5.35 g (0.0236 mol) of **29a** in 107 mL of ether causing a tan suspension to form. The suspension was stirred at room temperature for 3 h, then H_2O was added and the layers separated. The aqueous layer was washed twice with ether, then acidified with 10% H_2SO_4 and extracted twice with ether. The combined ether extracts were washed twice with 5% $NaHCO_3$, dried over $MgSO_4$, and concentrated to give 5.52 g (92%) of product as a red oil. An analytical sample was prepared by trituration with petroleum ether/ether: mp 123–125 °C. Anal. ($C_{16}H_{14}O_3$) C, H.

2,5,6-Trimethoxyfluorene-9-carboxaldehyde (30b). Ethyl formate (4.28 mL, 0.0560 mol) and $KOCH_3$ (3.72 g, 0.0502 mol) were reacted with 9.05 g (0.0353 mol) of **29b** for 5 h as described for **30a**. The reaction was worked up as described (except EtOAc used for extraction solvent) to yield 6.83 g (68%) of product: mp 165–171 °C. Anal. ($C_{17}H_{16}O_4$) C, H.

3,4-Dimethoxyfluorene-9-carboxaldehyde Oxime (31a). A solution prepared from 7.25 g (0.104 mol) of $NH_2OH·HCl$, 56 mL of H_2O, and 20.9 mL (0.104 mol) of 5 N NaOH was added to a solution of 5.30 g (0.0208 mol) of **30a** in 112 mL of EtOH. The resultant mixture was heated on a steam bath for 35 min, then filtered. The filtrate was diluted with H_2O to the cloud point and allowed to cool to room temperature overnight. The precipitated product was collected by filtration and washed with H_2O to give 4.17 g (74%) of product: mp 146–148 °C dec. Anal. ($C_{16}H_{15}NO_3$) C, H, N.

2,5,6-Trimethoxyfluorene-9-carboxaldehyde Oxime (31b). A suspension of 4.82 g (0.0170 mol) of **30b** in 72 mL of EtOH was reacted with 5 equiv of hydroxylamine as described for **31a**. An additional 40 mL of EtOH was added after heating to produce a solution, which was cooled to room temperature, then refrigerated overnight. The precipitated product was filtered and the filter cake suspended in H_2O. The suspension was filtered and the precipitate washed thoroughly with H_2O to give 4.29 g (85%) of product. An analytical sample was prepared by recrystallization from $EtOH/H_2O$: mp 152–155 °C. Anal. ($C_{17}H_{17}NO_4$) C, H, N.

3,4-Dimethoxy-9*H*-fluorene-9-methanamine (32a). A mixture of 2.15 g (7.98 mmol) of **31a**, 4.0 mL of $CHCl_3$, 0.25 g of PtO_2, and 200 mL of absolute EtOH was hydrogenated on a Parr shaker at 50 °C and 60 psi for 7 h. The cooled mixture was degassed, then additional EtOH was added and the mixture warmed to redissolve the precipitated product. The warm mixture was filtered and the filtrate concentrated to a white solid, which was recrystallized from EtOH to give 1.12 g (48%) of product in two crops: mp 265–268 °C dec; ^1H NMR ($CDCl_3/Me_2SO$-d_6) δ 3.28 (d, 2, $CHCH_2NH_2$), 3.90 (s, 3, OCH_3), 3.94 (s, 3, OCH_3), 4.33 (t, 1, $CHCH_2NH_2$), 6.90–8.10 (m, 6, ArH), 8.27 (br s, 3, $NH_2·HCl$). Anal. ($C_{16}H_{18}ClNO_2$) C, H, N.

2,5,6-Trimethoxy-9*H*-fluorene-9-methanamine (32b). A suspension of 3.28 g (0.0110 mol) of **31b** in 150 mL of EtOH was hydrogenated over Raney nickel at 50 °C for 3 h. The cooled suspension was degassed, filtered, and concentrated to 1.73 g of a red oil. The oil was dissolved in ether and treated with ethereal HCl to give 1.68 g of a bright yellow solid, which was recrystallized twice from EtOAc/EtOH to give 0.29 g (8.2%) of product as a white crystalline solid: mp 214–216 °C dec; ^1H NMR ($CDCl_3/Me_2SO$-d_6) δ 3.27 (d, 2, $CHCH_2NH_2$), 3.88 (s, 3, OCH_3), 3.89 (s, 3, OCH_3), 3.92 (s, 3, OCH_3), 4.30 (t, 1, $CHCH_2NH_2$), 6.78–7.94 (m, 5, ArH). Anal. ($C_{17}H_{20}ClNO_3$) C, H, N.

3,4-Dihydroxy-9*H*-fluorene-9-methanamine Hydrobromide (4a·HBr). Treatment of 0.80 g (3.1 mmol) of **32a** with 15.7 mmol of BBr_3 for 18 h as described for **1a** afforded 1.00 g of **4a** as a tan foam. An attempted crystallization from MeOH/EtOAc was unsuccessful; the solution was concentrated leaving a foam containing EtOAc and H_2O: ^1H NMR (Me_2SO-d_6) δ 3.30 (d, 2, $CHCH_2NH_2$), 4.21 (t, 1, $CHCH_2NH_2$), 6.89 (q, 2, ArH), 7.17–8.09 (m, 4, ArH); 3.28, 8.90, and 9.40 (br s's, D_2O exchangeable). Anal. ($C_{14}H_{14}BrNO_2·0.33C_4H_8O_2·0.25H_2O$) C, H, N.

2,5,6-Trihydroxy-9*H*-fluorene-9-methanamine Hydrobromide (4b·HBr). Treatment of 0.40 g (1.4 mmol) of **32b** with 7.0 mmol of BBr_3 for 18 h as described for **1a** afforded 0.36 g (80%) of **4b**: mp 269 °C dec; ^1H NMR (Me_2SO-d_6) δ 3.26 (m, 2, $CHCH_2NH_2$), 4.12 (t, 1, $CHCH_2NH_2$), 6.68–7.88 (m, 5, ArH); 7.88, 8.69, 9.30, and 9.43 (br s's, D_2O exchangeable). Anal. ($C_{14}H_{14}BrNO_3$) C, H, N.

Registry No. **1a**, 53622-74-5; **1a**·HBr, 103692-05-3; **1b**, 103692-23-5; **1b**·HBr, 103692-22-4; **1c**, 103692-21-3; **1c**·HBr, 103692-20-2; **1d**, 103692-25-7; **1d**·HBr, 103692-24-6; **3a**, 103692-10-0; **3a**·HBr, 103692-09-7; **3b**, 103692-36-0; **3b**·HCl, 103692-35-9; **3c**, 103692-34-8; **3c**·HBr, 103692-33-7; **3d**, 103692-38-2; **3d**·HCl, 103692-37-1; **4a**, 103692-53-1; **4a**·HBr, 103692-52-0; **4b**, 103692-55-3; **4b**·HBr, 103692-54-2; **5**, 82895-29-2; **6a**, 103692-04-2; **6b**, 103692-15-5; **7a**, 99424-04-1; **7b**, 99424-07-4; **8a**, 99424-71-2; **8a**·HCl, 99424-28-9; **8b**, 99424-74-5; **8b**·HCl, 99424-31-4; **8b** (*N*-benzyl), 103692-40-6; **8b** (*N*-benzyl)·HCl, 103692-39-3; **9**, 103692-06-4; **10**, 103692-07-5; **11a**, 103692-08-6; **11a**·HCl, 103692-30-4; **11b**, 103692-31-5; **11b**·HCl, 103692-32-6; **12**, 573-11-5; **12** (benzamide), 103692-11-1; **13**, 103692-12-2; **14a**, 99425-56-6; **14b**, 99425-57-7; **15a**, 103692-13-3; **15b**, 103692-14-4; **16a**, 93899-25-3; **16b**, 99425-66-8; **17a**, 99424-14-3; **17b**, 99424-17-6; **18a**, 103692-16-6; **18a**·(*d*-tartrate), 103692-18-8; **18b**, 103692-17-7; **18b**·(*d*-tartrate), 103692-19-9; **19a**, 103692-26-8; **19b**, 103692-27-9; **20a**, 103692-58-6; **21a**, 103692-28-0; **21b**, 103692-29-1; **25a**, 103692-41-7; **25b**, 103710-52-7; **26b**, 103692-42-8; **26b**·HCl, 103692-43-9; **28a**, 23346-81-8; **28b**, 103692-44-0; **29a**, 42523-19-3; **29b**, 103692-45-1; **30a**, 103692-46-2; **30b**, 103692-47-3; **31a**, 103692-48-4; **31b**, 103692-49-5; **32a**, 103692-56-4; **32a**·HCl, 103692-50-8; **32b**, 103692-57-5; **32b**·HCl, 103692-51-9; F_3CCONH_2, 354-38-1; propionaldehyde, 123-38-6; 2-amino-2-methyl-1-propanol, 124-68-5.