inhibition at various concentrations of inhibitor. Compounds were tested in batches of 3–20 per assay, and the results shown were obtained over a period of several years.

Human Prostatic 5α-Reductase. This assay was performed by modification of a previous procedure[29] that utilized rat prostate tissue. Human benign prostatic hypertrophy tissue that had been obtained by surgery and quickly frozen and stored at −70 °C served as the source of the enzyme. Typically, a 1.8-g portion was thawed, minced, and homogenized in 0.25 M sucrose buffer. The homogenate was centrifuged at 1200 rpm for 10 min, and the supernate was discarded. After the pellet was washed three times in buffer, it was suspended in buffer so that 1.0 mL contained about 300 mg of homogenized tissue. This suspension (0.1 mL) was incubated with 0.01 mL of inhibitor and 0.1 mL of a mixture containing [^{3}H]testosterone, unlabeled testosterone and dihydrotestosterone, glucose 6-phosphate, glucose-6-phosphate dehydrogenase, and NADP for 30 min at 37 °C. After the incubation, the steroids were extracted with 3.0 mL of ethyl acetate, and the organic phase was separated and evaporated under N_2. This extract was spotted onto TLC plates. After the TLC plates were developed in ethyl acetate–cyclohexane (1:1), the [^{3}H]DHT zone was scraped from the plate and counted. A control incubation without inhibitor and incubations with the standard inhibitor **10x** were run with each assay. The number of compounds run per assay ranged from one to 12. Generally, IC_{50} values were estimated from plots of inhibitory activity and then were compared to that obtained with **10x** in the same assay. These data are reported in Tables I–V.

Acknowledgment. We are indebted to Dr. Byron Arison and Herman Flynn for obtaining the 300-MHz NMR spectra and to Jack L. Smith for the mass spectra. Microanalytical data were obtained by the Analytical Research Department of Merck Sharp & Dohme Research Laboratories. We also acknowledge the helpful comments and encouragement of Dr. R. L. Tolman, Dr. B. G. Christensen, Dr. M. S. Glitzer, and Dr. E. H. Cordes. A special noted of thanks to MaryAnn Haas, who prepared the manuscript.

Supplementary Material Available: A table listing additional physical, analytical, and spectral (NMR, UV, and MS) data for compounds described in this paper (29 pages). Ordering information is given on any current masthead page.

Synthesis and Renal Vasodilator Activity of Some Dopamine Agonist 1-Aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diols: Halogen and Methyl Analogues of Fenoldopam

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Certain 6-halo-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines were found to be potent D-1 dopamine agonists. The 1-(4-hydroxyphenyl) analogues did not have central nervous system activity because their high polarity inhibited entry into the brain. However, these compounds were potent renal vasodilators. Fenoldopam, the 6-chloro analogue, is an especially significant member of the series, and its synthesis, pharmacology, and clinical properties have been studied extensively. The 6-methyl and 6-iodo congeners were potent renal vasodilators, but nonpotent partial D-1 agonists as measured by stimulation of rat caudate adenylate cyclase. A possible rationalization suggests different receptor reserves for these activities. The 9-substituted benzazepines were either inactive or of low potency as dopamine agonists, while the *N*-methyl analogues had significant antagonist potency as measured by inhibition of dopamine stimulation of rat caudate adenylate cyclase.

Elevated renal vascular resistance is found in most patients with essential hypertension[1,2] and is strongly implicated in both the pathogenesis and maintenance of this disease.[3] This suggested that selective renal vasodilators might be useful antihypertensive agents.[2] An approach to this type of agent via stimulation of renal dopamine receptors was suggested by the work of Goldberg[4,5] on the effects of dopamine on renal blood flow in α-adrenergic blocked dogs.

Dopamine is not suitable for general use as an antihypertensive agent. Its limitations include lack of oral absorption and its lack of selectivity because of activity at both D-1 and D-2 receptors as well as at norepinephrine receptors, which mediate both α- and β-adrenergic responses. Furthermore, although dopamine itself does not cross the blood–brain barrier, other dopamine agonists such as apomorphine and bromocriptine do pass the blood–brain barrier and cause biochemical and behavioral changes characteristic of central dopamine receptor activation.[6] The objective of our research in this area was the discovery of orally active dopamine agonist renal vasodilators selective for increasing renal blood flow without inducing central nervous system effects or responses due to activation of α- or β-adrenergic receptors. While this work was in progress, the concept of dopamine D-1 and D-2 receptor subtypes was developed[7] and a further objective that desirable compounds be D-1 agonists without significant D-2 activity was added. A major reason for this was to avoid the possibility of D-2-induced emesis. Apart

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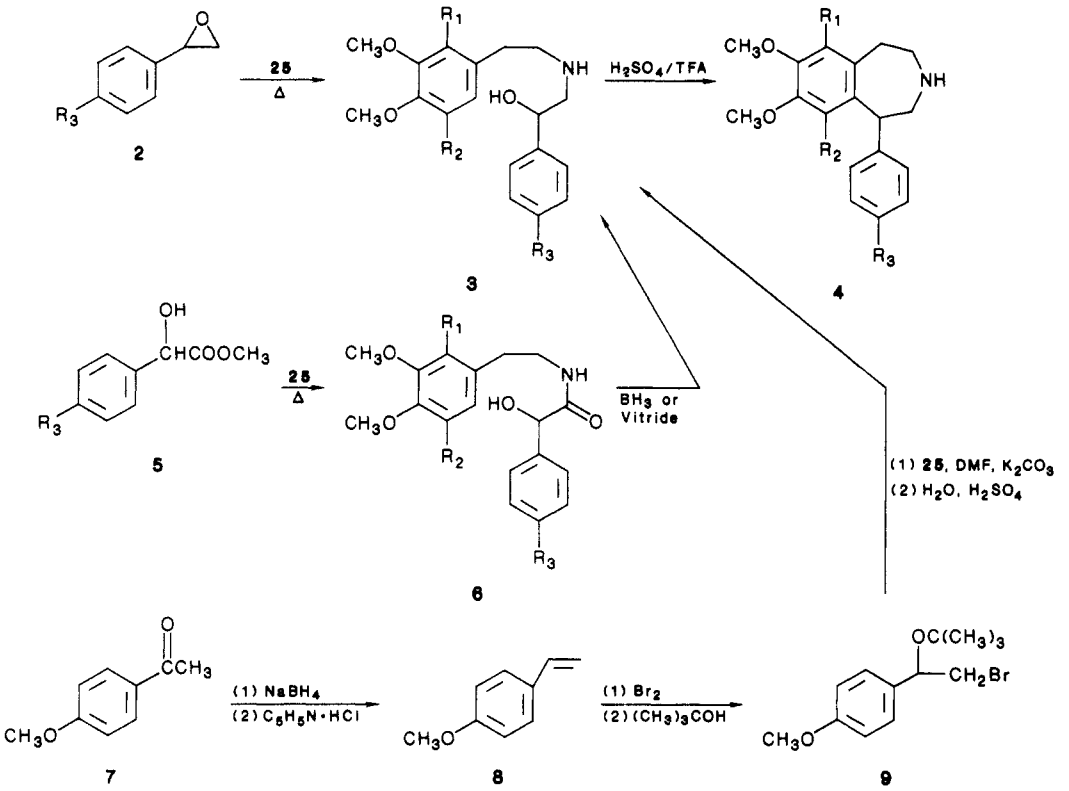
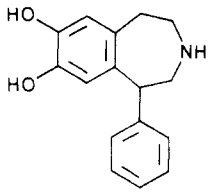
Scheme I. Synthesis of Benzazepines



from the D-1/D-2 classification, Goldberg[8] has proposed that peripheral cardiovascular dopamine receptors can be subdivided into two subtypes (DA_1 and DA_2) whose properties may be quite similar to the D-1 and D-2 receptors. In this paper the term D-1 implies also DA_1 unless specifically stated otherwise.

The first significant D-1 selective agonist identified in our laboratories was SK&F 38393 (1), which was orally active and was both a dopaminergic renal vasodilator[9] and a central dopamine agonist.[6] It was the first example of a D-1 agonist that does not have D-2 agonist activity.[10]



1

However, it has α effects as indicated by a phenoxybenzamine blockable pressor effect at high doses in the dog.[9] The goal of the work reported here was to modify the structure of 1 in such a manner as to produce a potent orally active D-1 renal vasodilator lacking significant α- or β-adrenergic activity, D-2 activity, or if dosed peripherally, central effects.[11]

Chemistry. Acid-catalyzed cyclization of the appropriate amino alcohols 3 as outlined in Scheme I provided a versatile synthesis of the required 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepines, 4.[12] Sulfuric acid in trifluoroacetic acid is an effective reaction system, and the low boiling point of the trifluoroacetic acid simplifies the workup of the reaction mixture. One method of obtaining the intermediate amino alcohols 3 is reaction of the appropriate styrene oxide 2 with a phenylethylamine 25. This reaction is complicated by the reaction of the amino alcohol with a second mole of styrene oxide to give bis-alkylation products and by reaction of the styrene oxide at the carbon atom α to the aromatic ring rather than at the desired β carbon. This was more pronounced with 4-methoxystyrene oxide, and is probably the result of a shift in the mechanism of the styrene oxide ring opening from S_N2 to S_N1 because of the increased stabilization of the *p*-methoxybenzyl carbonium ion.

An alternative synthesis of 3 that avoids the regioselectivity and bis-alkylation problems is reaction of the phenylethylamine 25 with the appropriate methyl mandelate 5 to give the mandelamide 6 followed by reduction of the amide to the amine. Reduction with lithium aluminum hydride or Vitride may cause loss of chlorine from the aromatic nucleus, while reduction with diborane may cause concomitant loss of the benzylic hydroxyl. Diborane reduction is preferable because it gives a more easily purified product.

A convenient large-scale preparation of the amino alcohol 3 that avoids these problems is also shown in Scheme I. Thus, for the preparation of 3 (R_1 = Cl, R_2 = H, and R_3 = OCH_3), *p*-methoxyacetophenone (7) was converted to *p*-methoxystyrene (8), which in turn was converted to the styrene dibromide. Bromination in methylene chloride even with careful control of the bromine-to-styrene ratio gave some aromatic ring bromination. However, this did not occur when the less reactive bromine–dioxane complex was used as the brominating agent. Solvolysis of the

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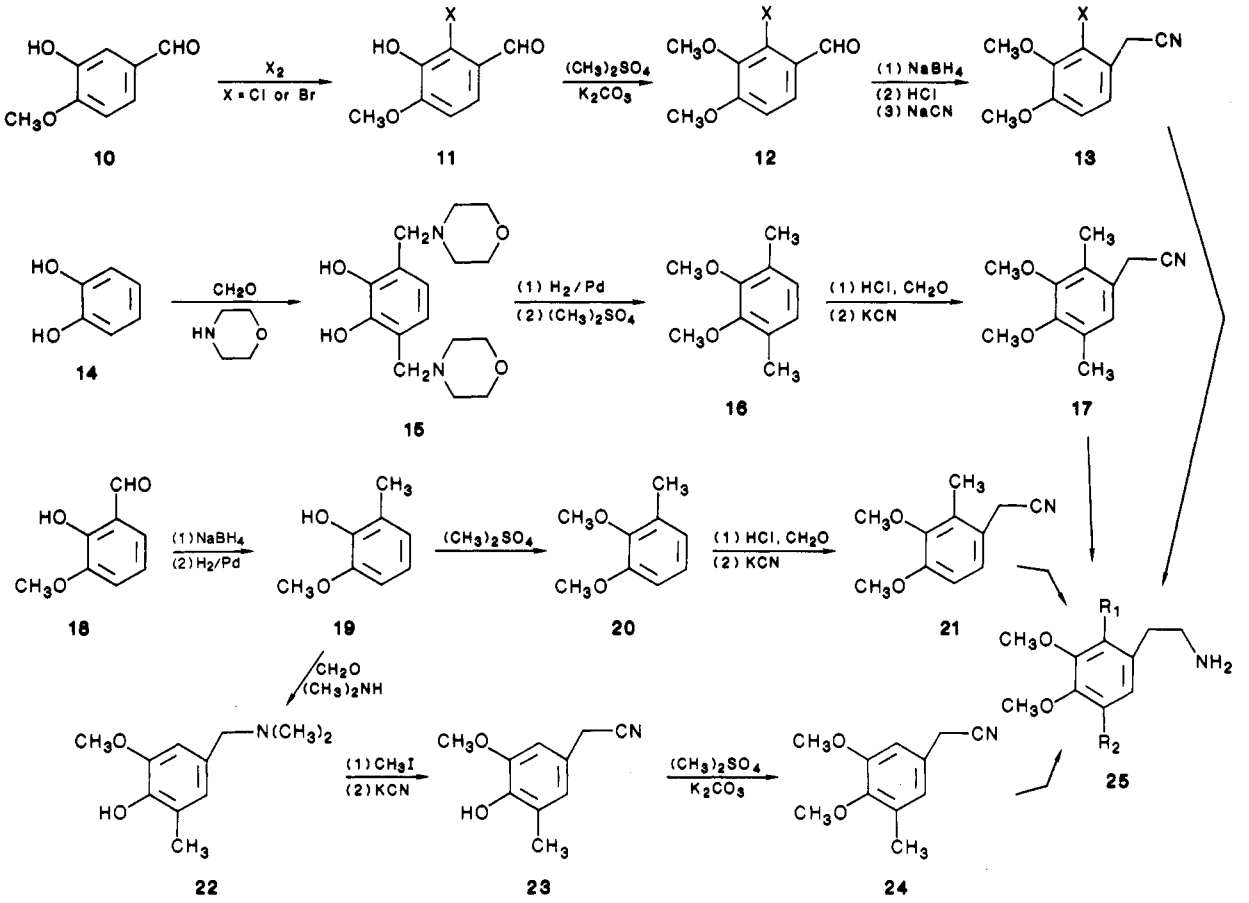
Scheme II. Preparation of Phenylethylamines



benzylic bromine in mildly alkaline *tert*-butyl alcohol gave the bromo ether **9**, which was allowed to react with (2-chloro-3,4-dimethoxyphenylethylamine (**25b**) to give the *tert*-butyl ether of the amino alcohol **3**. Acid hydrolysis cleaved the *tert*-butyl ether to give **3** (R_1 = Cl, R_2 = H, and R_3 = OCH_3).

Convenient syntheses of the (2-, 5-, and 2,5-substituted-3,4-dimethoxyphenyl)ethylamines (**25**) required for this work were developed where necessary and are shown in Scheme II. Thus the 2-chloro and 2-bromo compounds were prepared by halogenation of isovanillin (**10**) producing **11**, which was methylated to give the 2-haloveratraldehydes **12**. Reduction of the aldehydes by sodium borohydride, conversion of the resulting benzyl alcohols to the benzyl halides by aqueous HCl in an organic solvent, and treatment of these with sodium cyanide in a nonprotonic solvent gave the nitriles **13**. Reduction of these by diborane gave the amines **25**. Noteworthy is the halogenation ortho to both the phenol and the aldehyde groups. This reaction gives the desired product in good yield demonstrating the strong ortho activating effect of the phenol. 2-(3,4-Dimethoxy-2-methylphenyl)ethylamine (**25**; R_1 = CH_3, R_2 = H) was prepared starting with reduction of *o*-vanillin **18** to give **19**, which on methylation gave 3-methylveratrole **20**. Chloromethylation of this proceeded para to the less hindered methoxy group with high regiospecificity,[13] and the product was converted to the phenethylamine via **21** as described. The 5-methyl isomer was obtained by subjecting **19** to a Mannich reaction, which placed the (dimethylamino)methyl group para to the phenol affording **22**. Methylation of **22** gave the benzyltrimethylammonium salt, which on treatment with KCN gave the phenylacetonitrile **23**. This was methylated to give the veratrole **24**, which on hydrogenation gave the phenylethylamine (**25**; R_1 = H, R_2 = CH_3). 2-(3,4-Dimethoxy-2,5-dimethylphenyl)ethylamine (**25**; R_1 = R_2 = CH_3) was prepared by subjecting catechol **14** to a bis-Mannich reaction to give **15**, which on hydrogenolysis and methylation gave the dimethyl veratrole **16**. This was converted to the phenylethylamine via **17** by the same method. Convenient syntheses of 2-(2-fluoro- and 2,5-difluoro-3,4-dimethoxyphenyl)ethylamines have been described by Ladd et al.[14,15]

A number of benzazepines were obtained by transformations of other benzazepines as shown in Scheme III. Thus, bromination of **4** (R_1 = R_2 = R_3 = H) as the hydrochloride in acetic acid gave the 6-bromobenzazepine **27**. Contributing to the selectivity of this reaction was the insolubility of the desired product as the hydrobromide dibromide. The 6-bromobenzazepines were very valuable intermediates because the 6-lithio derivatives could be prepared by halogen–metal exchange. Thus, for example, **4** (R_1 = Br, R_2 = H, R_3 = OCH_3) was treated with trifluoroacetic anhydride to acylate the nitrogen, the amide treated with an excess of BuLi at −70 °C to effect the bromine–lithium exchange and convert the amide to an aminal, and this product treated with iodine to exchange the lithium for iodine. An acidic workup cleaved the protecting group from nitrogen and gave the desired secondary amine **28**.

The desired dopamine agonists are catechol derivatives. These were obtained from the corresponding methoxy derivatives by cleavage with boron tribromide in methylene chloride. Chlorination of the catechols at the 6- and 9-positions could be accomplished by oxidizing the catechol

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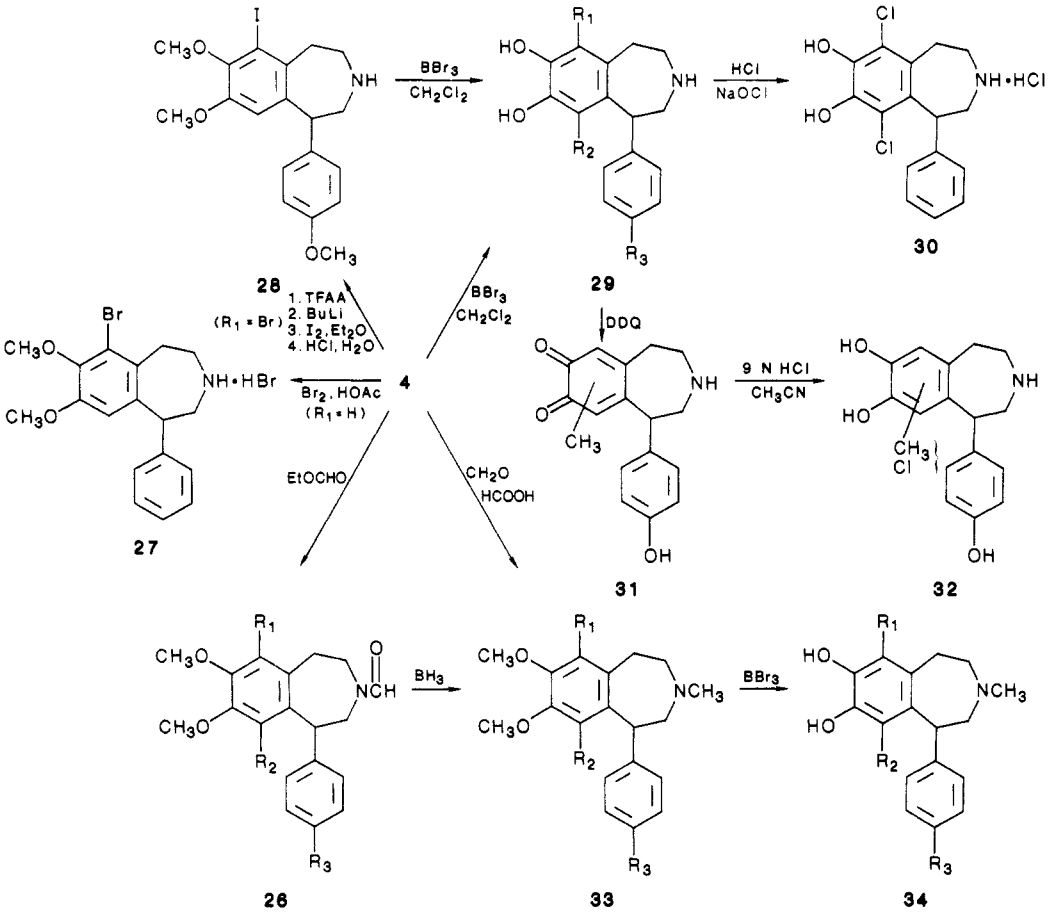
Scheme III. Transformation of Benzazepines



with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to the quinone followed by addition of hydrochloric acid to obtain the ring-chlorinated catechol. Application of this sequence to **29** (R_1 or R_2 = CH_3, R_2 or R_1 = H, R_3 = OH) proceeded via **31** to afford the corresponding 6(or 9)-methyl-9(or 6)-chlorobenzazepines **32**. The oxidation–HCl addition could be carried out twice in one pot using sodium hypochlorite–hydrochloric acid on 1 to obtain **30**. The *N*-methyl benzazepines **33** were obtained by the Clarke–Eschweiler reaction or by diborane reduction of the *N*-formyl benzazepine.

NMR spectroscopy was a useful diagnostic method for 8-methoxy- or 8-hydroxy-9-unsubstituted-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines. In these compounds the 9-hydrogen signal appears as a singlet peak near δ 6.4 ppm, the upfield shift being due to its location in the shielding cone of the 1-phenyl substituent. The consistent finding of the 9-hydrogen peak in this position suggests that the pseudo-equatorial 1-phenyl is a low-energy conformation in solution, which is in agreement with the solid-state structure of fenoldopam as determined by the single-crystal X-ray crystallographic method.[16]

The 1-aryl-7,8-dihydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepines are shown in Table II. Some 1-aryl-7,8-dimethoxy-2,3,4,5-tetrahydro-1*H*-3-benzazepines are shown in Table III, and some benzazepine precursors in Table IV.

Pharmacology. Renal vasodilator activity was determined in anesthetized dogs equipped with electromagnetic renal flow probes. Initial experiments were carried out using intravenous infusion rates of 3, 30, and 300 μg/kg per min each for 5 min. Compounds active in this protocol were subjected to more detailed evaluation in anesthetized dogs equipped to measure blood pressure by a transducer, heart rate by a cardiotachometer, and renal and iliac blood flow by electromagnetic flow probes.[17] Central nervous system (CNS) activity was assessed in vivo by determining drug-induced rotation in rats with 6-hydroxydopamine-induced lesions of the substantia nigra (SN_x rats) after either ip or intracaudal dosing.[17] D-1 activity was determined by measuring stimulation (agonist activity) or inhibition of dopamine-stimulated (antagonist activity) production of [^{14}C]cAMP from [^{14}C]ATP in homogenates of rat caudate nuclei.[17]

Results

The results obtained by testing the various 6-substituted derivatives of 2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine-7,8-diols are shown in Table I. In order to place these data in perspective, similar data are included for dopamine and **1**.[6,9,18] Dopamine is a potent renal vasodilator with good efficacy but exhibits modest selectivity with regard to effects on the iliac vascular resistance, blood pressure, and heart rate. Compound **1** is about one-tenth as potent as dopamine and causes only half as large a maximal effect on renal vascular resistance. This is in contrast to its central dopaminergic effects where on intracaudal dosing **1** is comparable to dopamine in causing

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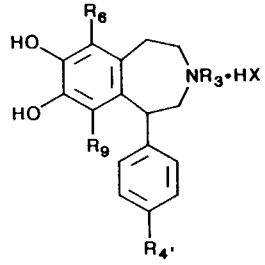
Table I. Cardiovascular, Renal, and Central Nervous System Testing of 6- and/or 9-Substituted-2,3,4,5-tetrahydro-1-phenyl (or 4-(hydroxyphenyl))-1*H*-3-benzazepine-7,8-diols



	structure					renal and cardiovascular activity, μg/kg, iv					CNS activity		adenylate cyclase	
						renal vasc res								inhibn, IC_{50} or
no.	6	9	4′	3	X	ED_{15} (*n*)	max % decr	IVR[b] ED_{30}	MABP[c] ED_{20}	HR[d] ED_{20}	RD_{500} [dose–turns], mg/kg, ip	RD_{500}, μg/rat, ic	stimuln EC_{50}, μM	% inhibn, μM
		dopamine				3.5 (8)	43	151	378	378		0.10, (0.08–1.3)	3.5	
1	H	H	H	H	Cl	35 (3)	18	735	1717	1050	0.7 (0.5–1.0)	0.18 (0.03–0.91)	0.08	
		(SK&F 38393)												
29a	F	H	H	H	Br	9 (2)	36	54000	54000	54000	[0.3–392 ± 123 turns]		0.04	31%, 1
											[1.0–814 ± 244 turns]			17%, 10
29b	Cl	H	H	H	Br	3.5 (2)	39	2918	6070	378	0.3 (0.21–0.75)	0.22 (0.07–1.55)	0.065	
29c	Br	H	H	H	Br	9 (3)	42	6075	6075	6075	0.34 (0.26–0.43)	[2.5 μg–472 ± 180 turns]	0.1	
29d	CH_3	H	H	H	Cl						1.28 (0.60–2.40)		0.1	
29e	CF_3	H	H	H	Cl						[10–839 ± 155 turns]			
30	Cl	Cl	H	H	Cl	10 (3)	59	6080	6080	6080	[10–496 ± 12 turns]		1.25	I[e] 10
29f	H	H	OH	H	Br						[10-I][e]	[1–532 ± 147 turns]	0.2	
29g	F	H	OH	H	Br	0.83 (4)	28	6064	6064	5.81 (decr.)			0.2	
29h	Cl	H	OH	H	CH_3SO_3	0.3 (5)	59	1820	1820	1820	[10-I]	0.5 (0.4–0.8)	0.048 (n = 5)	
		(fenoldopam)												
29i	Cl	H	OH[a]	H	Br	0.35 (2)	49	11.9	2125	360	[10-I]		0.045	
29k	Br	H	OH	H	Br	5 (2)	56	70	30360	30360	[10-I]		0.15	
29l	I	H	OH	H	Br	4.2 (4)	41	6060	6060	6060			36% DA at 10[g]	55%, 10
29m	CH_3	H	OH	H	CH_3SO_3	2.8 (3)	41	6060	6060	6060	[10–99 ± 33 turns]		30% DA at 10	50%, 10
29n	CF_3	H	OH	H	Cl	*f*	*f*	inactive secondary screen			[10-I]			
34a	Cl	H	H	CH_3	Cl	I 300 μg/kg/min (2)					0.03	0.32	30% DA at 10	0.6
34b	Br	H	H	CH_3	Br						0.015		30% DA at 10	0.32
34c	F	H	OH	CH_3	Br								36% DA at 10	55%, 10
34d	Cl	H	OH	CH_3	Br	MAP incr., RBF decr., 300 μg/kg/min (1)					[10–762 ± 253 turns]		22	1.4
34e	CH_3	H	H	CH_3	Br	I 300 μg/kg/min (1)					0.05		20% DA at 10	0.44
34f	H	H	H	CH_3	Cl	I 1000 μg/kg/stat (3)					0.1	0.06	20% DA at 10	0.63
29r	H	Cl	OH	H	Br	RVR and HR decreased at 300 μg/kg/min (2)							I 10	I 10
29o	H	CH_3	OH	H	Br	RBF increased, MAP, RVR, HR decreased at 300 μg/kg/min							I 10	I 10
29p	F	F	OH	H	Br	MAP, RBF, RVR increased at 300 μg/kg/min (2)							I 10	I 10
32a	Cl	Cl	OH	H	Cl	620 (5)	41	6200	6200	6200	[10-I]		2.6	
29q	CH_3	CH_3	OH	H	Br	RBF and HR increased at 300 μg/kg/min (2)							I 10	I 10
32b	CH_3	Cl	OH	H	Cl	30 (4)	42	6090	6090	6090			I 10	29%, 10
32c	Cl	CH_3	OH	H	Cl	RBF and HR increased at 3 μg/kg/min (2)							I 10	I 10

[a] 3′-Isomer. [b] Iliac vascular resistance. [c] Mean arterial blood pressure. [d] Heart rate. [e] I indicates no significant activity. [f] RBF up, RVR down at 3 μg/kg/min. [g] % dopamine response at 10 μM.

rotation in the lesioned rat (dopamine being protected with a monoamine oxidase inhibitor). Compound 1 is about 40 times more potent than dopamine in stimulating dopamine-sensitive adenylate cyclase in the rat caudate preparation. However, in this test 1 is only a partial agonist.

The 6-halo analogues of 1 (**29a–c**) are more potent than 1 as renal vasodilators by a factor of 3–9, have maximal effects similar to that of dopamine, and tend to increase renal vasodilator selectivity with regard to effects on iliac vascular resistance (IVR), mean arterial blood pressure (MABP), and heart rate (HR). These compounds display high CNS effects and are potent stimulators of adenylate cyclase. The 6,9-dichloro analogue **30** has less adenylate cyclase and less renal vasodilator potency than the 6-chloro analogues, but gives a larger renal vasodilator effect. The 6-methyl and 6-trifluoromethyl analogues are less active as renal vasodilators and show only weak CNS effects.

Introduction of a 4-hydroxyl substituent into the 1-phenyl ring has a marked effect on renal vasodilator potency in the 6-halo and 6-methyl analogues. Thus, although the 6-unsubstituted analogue **29f** is a vasoconstrictor and a weak stimulant of adenylate cyclase, the 6-halo and the 6-methyl analogues **29g,h,k–m** are potent renal vasodilators. The 6-chloro analogue **29h** (fenoldopam, SK&F 82526) is outstanding in both potency and efficacy. The 1-(3-hydroxyphenyl) analogue **29i**, although a potent renal vasodilator, is less selective than fenoldopam with respect to iliac vasodilation and heart rate. We find it surprising that within this series renal vasodilator activity is not well correlated with adenylate cyclase activity. Thus, the 6-iodo and 6-methyl analogues **29l,m** show only weak adenylate cyclase stimulant activity, but are renal vasodilators with potency and efficacy similar to that of dopamine. The 6-trifluoromethyl compound **29n**, like **29e**, is essentially inactive as a renal vasodilator. The 6-fluoro compound is unusual in that it causes a profound bradycardia without significant changes in blood pressure. Other data (not shown) suggest that this may be due to a D-2 or α-2 effect.[16] The 9-substituted and 6,9-disubstituted compounds in the 1-(4-hydroxyphenyl) series are not particularly active either as renal vasodilators or as stimulators of adenylate cyclase.

N-Methylation induces a striking conversion of these compounds into inhibitors of dopamine-stimulated adenylate cyclase. The antagonists have potent CNS activity as measured in the SN_x rat rotation test being active in the range of the corresponding D-1 agonists.

Another important finding is that introduction of the hydroxyl group into the 1-phenyl ring inhibits passage of the compound across the blood–brain barrier. Thus in the SN_x rat rotation test all the secondary amine compounds in this series are essentially inactive on ip administration, but both fenoldopam and **29f** are active on intracaudal administration. In the *N*-methyl series, the fenoldopam analogue has some activity on ip dosing suggesting that both the secondary amine and the phenolic hydroxyl contribute to inhibition of the passage of the benzazepines across the blood–brain barrier. Since CNS effects are undesirable in drugs intended for chronic cardiovascular therapy, this exclusion from the CNS is a critical part of the fenoldopam profile.

Discussion

Halogen and methyl substituents in the 6-position of 1-aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diols exert a profound influence on D-1 activity. Halogens, especially fluorine and chlorine, enhance potency substantially both in the in vitro D-1 stimulation of adenylate cyclase assay and in reduction of renal vascular resistance. The addition of a 4-hydroxy to the 1-phenyl group in this series substantially enhances renal vasodilator potency without causing corresponding increases in adenylate cyclase stimulation activity. This may reflect a difference between D-1 and DA_1 receptors, or it may be a consequence of the more polar 4-hydroxy compounds concentrating to a greater extent in the kidney. Evidence for different tissue distribution is seen in the relatively potent activity of the 1-phenyl series in the ip-dosed SN_x rat rotation test, while the members of the 1-(4-hydroxyphenyl) series are only active on intracaudal dosing. This suggests that these compounds do not readily cross the blood–brain barrier thus making these compounds less likely to exhibit CNS effects on peripheral dosing.

Compounds **29m** and **29l**, the 6-methyl and 6-iodo analogues of fenoldopam, are partial agonists and substantially less potent than fenoldopam in the adenylate cyclase test, but are similar in potency and efficacy to fenoldopam as renal vasodilators. Although it is possible that renal DA_1 receptors are different than D-1 striatal receptors, or that these compounds cause renal vasodilation by a non-dopaminergic mechanism, it appears more likely that these differences may merely reflect the activity of partial agonists in tissues with different receptor reserves.[19,20] Thus, in tissues with a large receptor reserve even a partial agonist may occupy enough receptor sites to cause a strong effector event to occur. In tissues with a low receptor reserve, which require full occupancy of receptor sites with agonist ligands for the maximum effector event to occur, a partial agonist will give a less than maximum effect. In this context, rat striatal membranes may have very little receptor reserve, and thus **29m** and **29l** cause only a weak stimulation of adenylate cyclase. On the other hand dog renal vascular tissue may have a large receptor reserve, and partial agonists can cause substantial renal vasodilation.

An interesting observation is the lack of potent adenylate cyclase or renal vasodilator activity in the 9-substituted compounds. A possible explanation is that bulk in this area makes the equatorial conformation of the 1-phenyl substituent unfavorable with respect to the axial conformation, and that the equatorial conformation is required for potent agonist activity. Another possible explanation is that the D-1 receptor has bulk intolerance in the area that would occupied by a 9-substituent as large as a chloro, but this bulk intolerance does not extend to the area occupied by the 1-phenyl substituent. This could be accommodated by a current conceptual model of the dopamine receptor.[21]

The objective of the work described in this paper was to discover a potent, orally active selective D-1 renal vasodilator. The outstanding compound found in the course of this work was fenoldopam (**29h**), and it is of interest to compare its properties with those desired for the target drug. In vitro fenoldopam stimulates adenylate cyclase, the classical D-1 response, with an EC_{50} of 57 nM making it 60 times more potent than dopamine. The receptor binding specificity of [^{3}H]fenoldopam was studied in rat striatal membranes by comparing the K_B for displacing [^{3}H]fenoldopam with the EC_{50} or K_i for stimulation or

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inhibition of dopamine-stimulated adenylate cyclase using a variety of D-1, D-2, and non-dopaminergic compounds.[22] The two activities showed a high correlation with high potency seen for D-1 nonselective antagonists *cis*-flupenthixol and (+)-butaclamol, and also the selective antagonists SCH 23390 and SK&F R-83566. Low potency for both activities was seen with D-2 antagonists such as domperidone and metoclopramide, providing in vitro evidence for D-1 selectivity. Non-dopaminergics such as phentolamine and propranolol also showed low potency for both activities.

Fenoldopam also exhibited potent dopamine agonist activity in vivo.[23] It increased renal blood flow and reduced renal vascular resistance on iv dosing in both anesthetized and conscious dogs, in anesthetized cynomolgus monkeys, and in anesthetized spontaneously hypertensive and Dahl salt-sensitive rats. It also reduced blood pressure in several of these preparations. Oral activity was demonstrated in renal clearance studies in conscious mannitol phosphate infused dogs. At 5 mg/kg po an 80% increase in estimated renal plasma flow lasting over 90 min occurred at 5 mg/kg. No incidence of D-2-mediated emesis was seen at any dose in this study, providing in vivo evidence for D-1 selectivity.

In normal human volunteers a single oral dose of 100 mg of fenoldopam increased estimated renal plasma flow by 50% and also increased urine volume and sodium excretion.[24] In essential hypertensive patients[25,26] decreases in blood pressure and total peripheral resistance with increases in renal blood flow were seen after oral doses of fenoldopam. Again absence of significant emesis provided evidence in man for lack of D-2 activity. Recent results suggest that fenoldopam, in addition to causing vasodilation by a direct effect on postsynaptic D-1 receptors on blood vessels, may also inhibit nerve-induced vasoconstriction by modulating D-1 receptors in sympathetic ganglia.[27,28] Thus, it is evident that fenoldopam may be useful not only in treating hypertension and in renal ischemia but also as an agent for studying D-1 receptors and the consequences of their stimulation in the periphery.

Experimental Section

Chemistry. Melting points were determined in open capillary tubes on a Thomas-Hoover or Mel Temp apparatus and are uncorrected. Elemental analyses were carried out by the Analytical, Physical and Structural Chemistry Department of Smith Kline & French Laboratories. Where analyses are reported by symbols of the elements, results were within 0.4% of the calculated values unless indicated otherwise. IR spectra were determined with a Perkin-Elmer 683 IR spectrophotometer; proton NMR spectra were determined with a Varian EM 390 90-MHz spectrometer. Many of the chemical transformations for the preparation of intermediates were routine, and the reaction products were readily characterized by NMR, IR, and TLC. In several of these cases unpurified intermediates were used to complete the syntheses. Examples of these reactions are reported in detail, and data for representative compounds are reported in the experimental tables. The complete compound number and methods for preparation of specific compounds are shown in the Tables II–IV.

***N*-[2-Hydroxy-2-(4-methoxyphenyl)ethyl]-2-(2-chloro-3,4-dimethoxyphenyl)ethylamine (3h). Via 4-Methoxystyrene Oxide.** A mixture of 2-(2-chloro-3,4-dimethoxyphenyl)ethylamine (32.5 g, 0.151 mol) and 4-methoxystyrene oxide (26.0 g, 0.173 mol) was heated on a steam bath with stirring under N_2 for 2.5 h. The cooled reaction mixture was triturated with hot benzene followed by petroleum ether. Recrystallization of the residue from an ethanol–petroleum ether mixture gave 10.3 g (19%) of a waxy yellow solid, mp 110–114.5 °C. TLC (10% MeOH–$CHCl_3$, SiO_2) showed trace impurities at R_f = 0.1 (starting amine) and R_f = 0.6 with the product as the major at R_f = 0.5. The product was used without further purification in the next step of the synthesis. A sample recrystallized from an ethanol–benzene mixture gave colorless crystals, mp 118.5–121 °C. Anal. ($C_{19}H_{24}ClNO_4$) C, H, N, Cl.

Via Mandelamide Reduction. A solution of 690 g (1.82 mol) of **6h** in 3.45 L of sieve-dried THF was added over a 45-min period to 3.38 L of 0.94 M BH_3 (3.18 mol) in THF at 10–12 °C under nitrogen. This mixture was refluxed for 30 min, and then 1.38 L of methanol was added slowly with cooling. The solution was concentrated under vacuum and the residue was dissolved in MeOH and again concentrated to dryness. The residue was dissolved in 2.7 L of methanol; 0.70 L of 20% aqueous H_2SO_4 was added, and the mixture was refluxed for 1 h. The solution was made basic with 40% NaOH with cooling and diluted with water, and the solid product was collected by filtration and washed with water. Recrystallization from a mixture of ethanol and ether gave 263 g (40%) of colorless crystals, mp 115–117 °C. Byproducts isolated from the reaction mixture were identified as des-hydroxy **3h** and des-hydroxy **6h** by comparison with authentic samples.

Via 9. A mixture of 2-(2-chloro-3,4-dimethoxyphenyl)ethylamine (50 g, 0.232 mol), **9** (83.2 g, 0.290 mol), powdered anhydrous K_2CO_3 (96.1 g. 0.696 mol), and 175 mL of sieve-dried DMF was stirred at 110 °C for 2 h in a nitrogen atmosphere. The reaction mixture was diluted with H_2O (1 L) and extracted with EtOAc, and the organic layer was washed with saturated brine, dried over Na_2SO_4, and concentrated to give a viscous tan oil, which is the *tert*-butyl ether of **3h**. This was heated with vigorous stirring on a steam bath with 10% H_2SO_4 (500 mL), and the reaction mixture was made basic with 40% NaOH to give a tan semisolid product. The reaction mixture was extracted with CH_2Cl_2 (300 mL) and the organic layer washed with water and dried over $MgSO_4$. Concentration gave a tan solid, which when recrystallized from an EtOH–petroleum ether mixture gave 45.2 g (53%) of product, mp 116–118 °C, which on TLC (MeOH–$CHCl_3$, SiO_2) showed no visible impurities.

***N*-(2-Chloro-3,4-dimethoxyphenylethyl)-4-methoxymandelamide (6h).** A mixture of 2-(2-chloro-3,4-dimethoxyphenyl)ethylamine (118.7 g, 0.55 mol) and methyl 4-methoxymandelate (102.8 g, 0.524 mol) was stirred on a steam bath under a nitrogen atmosphere for 18 h. The cooled reaction mixture was dissolved in CH_2Cl_2 and washed twice with 10% HCl and once with H_2O and 5% $NaHCO_3$. Concentration of the dried ($MgSO_4$) solution under vacuum gave 183 g of a yellow oil, which when triturated with ether gave 99 g (50.7%) of a solid, mp 69–72 °C. Anal. ($C_{19}H_{22}ClNO_5$) C, H, N, Cl.

2-(2-Chloro-3,4-dimethoxyphenyl)ethylamine (25b). Isovanillin was chlorinated by the method of Faulkner and Woodcock[29] to give 2-chloroisovanillin (**11b**): mp 198–203 °C, in 90% yield [reported[29] mp 205–206 °C]. A suspension of **11b** (56.3 g, 0.302 mol) and K_2CO_3 (104 g, 0.75 mol) in DMF (300 mL) was stirred for 10 min, and then dimethyl sulfate (57.8 g, 0.458 mol) was added over a 10-min period. The reaction mixture was heated on a steam bath for 5 min; 20 mL of water was added, and the heating continued for an additional 5 min. The reaction mixture was poured into 500 mL of water, and the crystals were collected and recrystallized from acetic acid to give 40 g (66%) of **12b**: mp 69.5–70.5 °C [lit.[30] mp 69–70]. In other experiments the crude material, mp 68–70 °C, which was obtained in 90% yield was used in the next step. $NaBH_4$ (18.93 g, 0.5 mol) was added to a slurry

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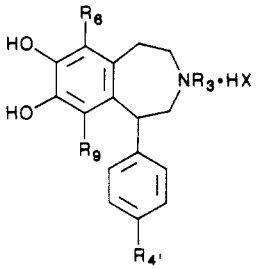
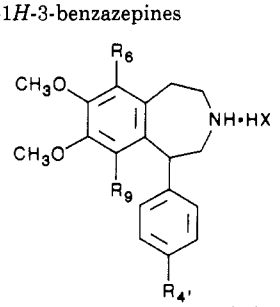
Table II. 1-Aryl-2,3,4,5-tetrahydro-1*H*-3-benzazepine-7,8-diols



no.	structure 6	9	4′	3	X	method[a]	mp, °C	recrystn[b] solvent	formula[c]
29a	F	H	H	H	Br	1	285–289 dec	A	$C_{16}H_{16}FNO_2$·HBr
29b	Cl	H	H	H	Br	1	259–260	E	$C_{16}H_{16}ClNO_2$·HBr
29c	Br	H	H	H	Br	6	240–242	D	$C_{16}H_{16}BrNO_2$·HBr
29d	CH_3	H	H	H	Br	1	160–163	F	$C_{17}H_{19}NO_2$·HBr·0.5H_2O
29e	CF_3	H	H	H	Cl	*e*			
30	Cl	Cl	H	H	Cl	5	185–200 dec	F	$C_{16}H_{15}Cl_2NO_2$·HCl·1.25H_2O
29f	H	H	OH	H	Br	9	287–289	A	$C_{16}H_{17}NO_3$·HBr·0.5H_2O
29g	F	H	OH	H	Br	2	275 dec	A	$C_{16}H_{16}FNO_3$·H_2O
29h	Cl	H	OH	H	MS[d]	3	272 dec	A	$C_{16}H_{16}ClNO_3$·CH_3SO_3H
29i	Cl	H	3′-OH	H	Br	*f*			
29k	Br	H	OH	H	Br	1	254 dec	B	$C_{16}H_{16}BrNO_3$·HBr
29l	I	H	OH	H	Br	7	239–240 dec	F	$C_{16}H_{16}INO_3$·HBr
29m	CH_3	H	OH	H	MS[d]	3	287–290	A	$C_{17}H_{19}NO_3$·CH_3SO_3H
29n	CF_3	H	OH	H	Cl	*e*			
29r	H	Cl	OH	H	Br	3	foam	G	$C_{16}H_{16}ClNO_3$·HBr·2H_2O
29o	H	CH_3	OH	H	Br	2	232–242	A	$C_{17}H_{19}NO_3$·HBr·0.5H_2O
29p	F	F	OH	H	Br	2	foam	G	$C_{16}H_{15}F_2NO_3$·HBr·0.5H_2O·0.5EtOAc
29q	CH_3	CH_3	OH	H	Br	2	266–268	A	$C_{18}H_{21}NO_3$·HBr
32a	Cl	Cl	OH	H	Cl	4	216–221 dec	I	$C_{16}H_{15}Cl_2NO_3$·HCl·1.25H_2O
32b	CH_3	Cl	OH	H	Cl	4	213 dec	C	$C_{17}H_{18}ClNO_3$·HCl·0.5H_2O
32c	Cl	CH_3	OH	H	Cl	4	212 dec	A	$C_{17}H_{18}ClNO_3$·HCl
34a	Cl	H	H	CH_3	Cl	*f*			
34b	Br	H	H	CH_3	Br	8	181–183	H	$C_{17}H_{18}BrNO_2$·HBr·0.5H_2O
34c	F	H	OH	CH_3	Br	8	282 dec	B	$C_{17}H_{18}FNO_3$·HBr
34d	Cl	H	OH	CH_3	Br	8	275 dec	A	$C_{17}H_{18}ClNO_3$·HBr
34e	CH_3	H	H	CH_3	Br	8	168–170	F	$C_{18}H_{21}NO_2$·HBr·0.5H_2O
34f	H	H	H	CH_3	Cl	*g*			

[a] Synthetic pathways: 1, **2** → **3** → **4** → **29**; 2, **5** → **6** → **3** → **4** → **29**; 3, **7** → **8** → **9** → **3** → **4** → **29**; 4, **29** → **31** → **32**; 5, **29** → **30**; 6, **26** → **27** → **29**; 7, **26** → **28** → **29**; 8, **26** → **33** → **34**. [b] Recrystallization solvents: A, MeOH–EtOAc; B, MeOH–EtOAc–pet ether; C, EtOAc trituration; D, H_2O then CH_3CN trituration; E, H_2O then EtOAc trituration; F, H_2O; G, chromatography SiO_2, 5 → 25% MeOH–CH_2Cl_2; H, MeOH; I, 1.2 N HCl. [c] All of the compounds gave satisfactory analyses for C, H, and N except **29p**, which was noncrystalline. Calcd: C, 48.99; H, 4.80; N, 3.17. Found: C, 48.51; H, 4.18; N, 3.15. In addition, **30** gave a satisfactory analysis for Cl and **29h** satisfactory analyses for S and Br. [d] Methanesulfonic acid salt. [e] Reference 32. [f] Reference 33. [g] Reference 34.

Table III. 7,8-Dimethoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines

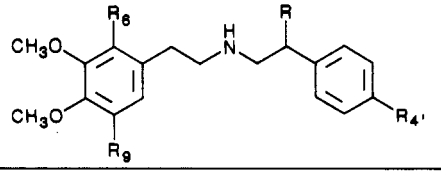


no.	structure 6	9	4′	X	method[a]	% yield	mp, °C	recrystn[b] solvent	formula[c]
4c	Br	H	H	Cl	2	77	236–238	A	$C_{18}H_{20}BrNO_2$·HCl
4d	CH_3	H	H	Cl	1	97	223–226	B	$C_{19}H_{23}NO_2$·HCl
4f	H	H	OCH_3	Br	1	60	213	C	$C_{19}H_{23}NO_3$·HBr
4g	F	H	OCH_3		1	71	80–83	D	$C_{19}H_{22}FNO_3$
4h	Cl	H	OCH_3		1	53	140–143.5	G	$C_{19}H_{22}ClNO_3$
4k	Br	H	OCH_3		1	79	140–141.5	H	$C_{19}H_{22}BrNO_3$
4m	CH_3	H	OCH_3		1	76	79.5–84	F	$C_{20}H_{25}NO_3$

[a] Methods: 1, TFA, H_2SO_4; 2, **26** → **27**. [b] Recrystallization solvents: A, MeOH–Et_2O; B, triturate Et_2O; C, MeOH–EtOAc; D, chromatography, 0–10% MeOH–CH_2Cl_2, SiO_2; E, EtOH–pet ether; F, oil crystallized on standing; G, EtOAc; H, chromatography 0–5% MeOH–$CHCl_3$, SiO_2. [c] All of the compounds gave satisfactory analyses for C, H, and N; **4c** analyzed correctly for Br and **4h** correctly for Cl.

of **12b** (200.6 g, 1.0 mol) in 1.5 L of 95% ethanol while keeping the temperature below 25 °C. After stirring for 1 h, acetone (100 mL) was added with cooling, and the reaction mixture was concentrated to 800 mL under vacuum and poured into 2 L of water. Extraction with CH_2Cl_2 and concentration of the dried organic phase gave 205 g (100%) of the benzyl alcohol as a colorless solid,

Table IV. *N*-(2-Aryl-2-hydroxyethyl)-2-(3,4-dimethoxyphenyl)ethylamines



no.	structure 6	9	4′	R	method[a]	% yield	mp, °C	recrystn[b] solvent	formula[c]
3a	F	H	H	OH	1	39	59–64	A	$C_{18}H_{22}FNO_3$
3b	Cl	H	H	OH	1	37	100–101	B	$C_{18}H_{22}ClNO_3$
3d	CH_3	H	H	OH	1	40	113.5–115	C	$C_{19}H_{25}NO_3$
3f	H	H	OCH_3	OH	1	21	92	D	$C_{19}H_{25}NO_4$
3g	F	H	OCH_3	OH	3	63	99–101.5	C	$C_{19}H_{24}FNO_4 \cdot 0.25H_2O$
3h	Cl	H	OCH_3	OH	1, 2, 3	*d*	118.5–121	F	$C_{19}H_{24}ClNO_4$
3k	Br	H	OCH_3	OH	1	18	116.5–118	C	$C_{19}H_{24}BrNO_4$
3m	CH_3	H	OCH_3	OH	3	67	129–130	E	$C_{20}H_{27}NO_4$
3r	H	Cl	OCH_3	OH	3	92	91–92.5	C	$C_{19}H_{24}ClNO_4$
	CH_3	H	OCH_3	*t*-BuO	4	92	oil	G	$C_{24}H_{35}NO_4$

[a] Methods: 1, **2** → **3**; 2, **6** → **3**; 3, **9** → **3**; 4, **9** → **3** precursor. [b] Recrystallization solvents: A, chromatography EtOAc, SiO_2; B, EtOAc, pet ether; C, EtOH, pet ether; D, EtOAc, hexane; E, chromatography, 0–10% MeOH–CH_2Cl_2, SiO_2; F, benzene, pet ether; G, chromatography, 0–3% MeOH–CH_2Cl_2, SiO_2. [c] All of the compounds gave satisfactory analysis for C, H, N; **3h** and **3k** also gave satisfactory analyses for Cl and Br. [d] See Experimental Section.

mp 67–70 °C. This alcohol (203 g, 1 mol) was dissolved in benzene (1 L) and shaken with 500 mL of 12 N HCl for 5 min in a separatory funnel. The aqueous layer was extracted with benzene, and the combined organic layers were washed with water and concentrated to give 214.4 g (97%) of the benzyl chloride as a brown liquid, which crystallized on standing and which was used without further purification. This compound (214.4 g, 0.97 mol) was dissolved in 1 L of Me_2SO; NaCN (59.4 g, 1.21 mol) was added, and the mixture was stirred for 1.25 h. The mixture was poured into 1 L of water and extracted with ether, and the dried ether layer was concentrated under vacuum to give 197.5 g (96%) of **13b** as a tan oil, which crystallized on standing: mp 53.5–56 °C [lit.[13] mp 65–65.5 °C]. A solution of **13b** (169.7 g, 0.80 mol) in 600 mL of THF was added slowly to a solution of 0.94 M borane in THF (1700 mL, 1.56 mol) under argon; the reaction mixture was refluxed for 1.5 h and cooled, and 250 mL of MeOH was added. After an additional 0.5 h reflux, the solution was concentrated under vacuum and the residue dissolved in dilute HCl, washed with ether, made basic with 40% NaOH, and extracted with CH_2Cl_2. The extract was washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated to give 128.5 g (74%) of a yellow oil (**25b**), which solidified on cooling. This product was also obtained by catalytic reduction of **13b** over Raney Ni in methanol saturated with anhydrous NH_3.

4-Methoxystyrene (8). A solution of 1200 g (7.99 mol) of 4-methoxyacetophenone in 2.4 L of methanol was treated with 151 g (3.99 mol) of $NaBH_4$ added portionwise while keeping the reaction temperature below 25 °C. The reaction mixture was diluted with 4.8 L of H_2O and extracted twice with CH_2Cl_2, and the organic layer was washed with water and dried over $MgSO_4$. Concentration under vacuum gave 1201 g (98%) of an oil, which showed a single component on TLC ($CHCl_3$–silica) and whose NMR was consistent with that of 1-(4-methoxyphenyl)ethanol. Pyridine (1.75 L, 21.6 mol) was placed in a 12-L flask equipped with a mechanical stirrer and a distillation head. After addition of 1.93 L (23.1 mol) of 12 N HCl, 1800 mL of a pyridine–water mixture was removed by distillation resulting in a pot temperature of 218 °C. After addition of another 2.18 L (27 mol) of pyridine and removal of 200 mL of distillate, *tert*-butylhydroquinone (3 g) and 1-(4-methoxyphenyl)ethanol (2731 g, 18 mol) were added rapidly and an additional 700 mL of distillate, bp 100–110 °C, removed. The pot temperature was maintained at 125 °C for 1.5 h and then cooled to 25 °C by addition of 6 L of ice. The reaction mixture was extracted with petroleum ether (3 × 4 L) and the organic phase washed with water, 5% $NaHCO_3$, three times with 2 L of 5% HCl, 5% $NaHCO_3$, and saturated saline. After drying over $MgSO_4$, concentration of the solvent under vacuum while keeping the pot temperature below 35 °C gave 1638 g (68%) of material containing 8% petroleum ether as determined by NMR. Distillation of a similar reaction product starting with 3040 g (20 mol) of alcohol gave 1558 g (58.1%) of a colorless oil, bp 95 °C (16 torr).

1-(4-Methoxyphenyl)-1,2-dibromoethane. A solution of 8 (241 g, 1.80 mol) in 480 mL of CH_2Cl_2 was treated over a 2-h period with a solution of CH_2Cl_2 (660 mL), dioxane (242 mL), and Br_2 (98 mL, 1.9 mol) while the temperature was held at −5 to 0 °C. When the Br_2 color persisted for a few minutes, the addition of dioxane dibromide was stopped and the reaction mixture concentrated under vacuum to give a pasty solid. Isooctane (200 mL) was added and the mixture again concentrated under vacuum. The residue was recrystallized from hexane to give 457 g (86.4%) of product, mp 76–80 °C, which by VPC analysis was 99.91% pure. It contained 0.09% of **8** and no detectable amount of ring-brominated product.

2-Bromo-1-(*tert*-butoxy)-1-(4-methoxyphenyl)ethane (9). *tert*-Butyl alcohol (5.5 L, 58 mol) was dried by removing a 500-mL portion by distillation. To the slightly cooled solvent anhydrous powdered $MgSO_4$ (794 g, 6.59 mol), MgO (132 g, 3.28 mol), and 1-(4-methoxyphenyl)-1,2-dibromoethane (882 g, 3.0 mol) were added and the reaction mixture refluxed for 75 min. TLC (CH_2Cl_2–hexane, 1:1, silica) showed the absence of the dibromoethane (R_f = 0.15) and the product (R_f = 0.70) as the only major component. After cooling, CH_2Cl_2 (2 L) was added and the solids were removed by filtration and washed with CH_2Cl_2. The filtrate was concentrated under vacuum at 60 °C, and the residue was dissolved in hexane (4.5 L) and washed with water and 5% $NaHCO_3$, and dried over $MgSO_4$. Removal of the solvent at 50 °C left 843 g (97.8%) of product, which by VPC (1% OV-225, 125 °C) was 95% pure and was used without further purification.

6-Chloro-2,3,4,5-tetrahydro-7,8-dimethoxy-1-(4-methoxyphenyl)-1*H*-3-benzazepine (4h). A solution of **3h** (787 g, 2.15 mol) in TFA (5900 mL) was treated at 25 °C with 36 N H_2SO_4 (179 mL, 3.225 mol) and then stirred for 3.5 h at 25 °C. Anhydrous NaOAc (793 g, 9.67 mol) was added, which raised the pot temperature to 60 °C. The reaction mixture was concentrated at less than 55 °C under vacuum, and the residue was diluted with water and made basic with 14 N NH_4OH with cooling. The mixture was extracted with CH_2Cl_2, and the organic layer was dried over $MgSO_4$ and concentrated under vacuum to give a yellow solid. Recrystallization from EtOAc (1.9 L) and washing the product with ether gave 517 g (69%) of crystals, mp 140–143.5 °C. Anal. ($C_{19}H_{22}ClNO_3$) C, H, N, Cl.

6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol Methanesulfonate (29h). A solution of BBr_3 (825 g, 3.29 mol) in CH_2Cl_2 (1 L) was added to a solution of **4h** (229 g, 0.659 mol) in CH_2Cl_2 (2.3 L, sieve dried) kept near 15 °C. The reaction mixture was stirred at 25 °C for 3 h, and then 1.65 L of methanol was added slowly while the reaction temperature was held at −20 °C. The reaction mixture was then concentrated under vacuum, the residue triturated with warm

EtOAc, and the product collected by filtration to give 240.7 g (95%) of a light-tan solid, mp 277 °C dec. Anal. ($C_{16}H_{16}ClNO_3$·HBr) C, H, N. The hydrobromide (228.7 g, 0.591 mol) was dissolved in methanol (3.56 L) and the solution divided into two equal portions. Each portion was added slowly to 2 L of 5% $NaHCO_3$ while keeping the temperature below 23 °C by the addition of ice. The solid free base was collected by filtration, washed with water, and the damp product from both portions was combined and suspended in MeOH, and 46 mL (0.709 mol) of methanesulfonic acid was added to give a solution. This was concentrated under vacuum until crystallization started. After chilling the suspension, the product was collected and washed with EtOAc and then Et_2O to give 106 g (45%) of a colorless solid, mp 271 °C dec. Concentration of the mother liquors to dryness gave a solid that was dissolved in boiling methanol and crystallized by addition of EtOAc and chilling. The solid was collected and washed with EtOAc and then Et_2O to give an additional 84.1 g (35%) of a colorless solid, mp 270 °C, identical with the first crop by TLC (EtOAc–MeOH–NH_4OH, 75:23:2, SiO_2), NMR, IR, and elemental analysis. Anal. ($C_{17}H_{20}ClNO_6S$) C, H, N, S, Br.

(2-Bromo-3,4-dimethoxyphenyl)ethylamine (25c). 2-Bromoisovanillin was prepared in 36% yield by the method of Hazlet and Brotherton.[31] Methylation by the procedure used for preparing **12b** gave **12c**: mp 81–83 °C in 80% yield [lit.[30] mp 85–85.5 °C]. Reduction of this with $NaBH_4$ as described for **12b** gave 2-bromo-3,4-dimethoxybenzyl alcohol, mp 74–76 °C. Anal. ($C_9H_{11}BrO_3$) C, H, Br. This alcohol was converted to the benzyl chloride and then (2-bromo-3,4-dimethoxyphenyl)acetonitrile (**13c**) in 90% yield as described for **13b**. Diborane reduction as described for **13b** gave **25c** in 60% yield. The hydrochloride was recrystallized from an ethanol–hexane mixture to give colorless crystals, mp 208–209.5 °C. Anal. ($C_{10}H_{14}BrNO_2$·HBr) C, H, N, Br.

(5-Chloro-3,4-dimethoxyphenyl)ethylamine (25r). A solution of 5-chloro-3,4-dimethoxybenzaldehyde (80 g, 0.40 mol) in 600 mL of 95% ethanol was treated with 7.57 g (0.20 mol) of $NaBH_4$ while keeping the temperature at 25 °C. After 1 h, acetone (40 mL) was added and the filtered solution concentrated under vacuum. The residue was partitioned between water and CH_2Cl_2, and the organic layer was washed with water and concentrated to give 66.9 g (82%) of a yellow oil whose NMR and IR spectra were consistent with those of the benzyl alcohol. A mixture of 63.4 g (0.313 mol) of the benzyl alcohol dissolved in 275 mL of toluene and 150 mL of 12 N HCl was stirred on a steam bath for 1 h; the layers were separated, and the toluene layer was washed 5 times with 75 mL of water. The organic phase was concentrated under vacuum, and the residue was dissolved in CH_2Cl_2, dried over $MgSO_4$, concentrated, and then distilled to give 52.89 g (76%) of a colorless oil, bp 102–107 °C (0.17–0.3 torr), whose NMR and IR spectra were consistent with those of the benzyl chloride. Anal. ($C_9H_{10}Cl_2O_2$) C, H, Cl. The benzyl chloride (48.8 g, 0.221 mol) and NaCN (13.52 g, 0.276 mol) were dissolved in 250 mL of sieve-dried Me_2SO, stirred for 1 h, poured into 1 L of water, and extracted with Et_2O. Concentration and distillation of the dried ether extract gave 39.27 g (84%) of a colorless oil, bp 116–123.5 °C (0.15 torr), whose NMR and IR spectra were consistent with those of the nitrile. A solution of this oil (34.3 g, 0.16 mol) in THF was treated with 343 mL of 1 M BH_3 in THF. Workup in the usual manner gave 23.12 g (66%) of a colorless liquid whose NMR and IR spectra were consistent with those of the amine. Treatment of 2.64 g of this amine in ether with ethanolic HCl gave 2.77 g (90%) of the hydrochloride as white crystals, mp 186–192 °C. Anal. ($C_{10}H_{14}ClNO_2$·HCl) C, H, N.

6,9-Dichloro-2,3,4,5-tetrahydro-1-phenyl-1*H*-3-benzazepine-7,8-diol Hydrochloride (30). To a slurry of **1** (29.1 g, 0.100 mol) in 470 mL of 9 N HCl kept below 30 °C by cooling was added dropwise over a 40-min period 329 mL of 5.25% NaOCl. The deep-red mixture was stirred at ambient temperature for 5 h; $NaHSO_3$ (10 g) was added in portions, and the mixture was stirred for 16 h. Filtration gave 33.3 g of a powder, which was recrystallized from 165 mL of H_2O to give 10.3 g (28%) of **30** as a white powder, mp 185–200 °C dec.

6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-9-methyl-1*H*-3-benzazepine-7,8-diol Hydrochloride (32c). A mixture of 1.22 g (5.37 mmol) of DDQ in 94 mL of CH_3CN was added over a 15-min period to a suspension of **29o** (1.10 g, 3.42 mmol) in 47 mL of 9 N HCl to give a dark-red solution, which was allowed to stand at ambient temperature for 16 h. Solid $NaHSO_3$ was added to discharge the color; the insoluble salts were removed by filtration, and the filtrate was concentrated under vacuum to near dryness. The residue was treated with 150 mL of H_2O and then heated on a steam bath for 15 min and filtered, and 15 mL of 12 N HCl was added to the filtrate. Chilling for 2 h gave a small amount of solid, which was removed by decantation. Concentration to a small volume gave a solid that was collected, washed with a small volume of cold H_2O, and recrystallized from MeOH–EtOAc to give 1.08 g (62%) of a tan solid: mp 212 °C dec; MS, *m/e* 319; TLC (EtOAc–acetone–AcOH–H_2O, 50:20:10:10, silica GF) showed a single component.

6-Bromo-2,3,4,5-tetrahydro-7,8-dimethoxy-1-phenyl-1*H*-3-benzazepine Hydrochloride (4c). Bromine (10 g, 0.063 mol) was added dropwise to a solution of **26**·HCl ($R_1 = R_2 = R_3 = H$) (10 g, 0.031 mol) in 75 mL of glacial AcOH, and the reaction mixture was stirred for 2 h. The solid that formed was then collected, washed with ether, dissolved in 100 mL of methanol, and treated with acetone to remove residual bromine. An excess of ethereal HCl was added, the solution concentrated, and the residue redissolved in methanol and HCl and again concentrated. After another cycle of MeOH–HCl, the residue was recrystallized from CH_3OH–Et_2O to give 9.6 g (77%) of **27**, mp 236–238 °C. Anal. ($C_{18}H_{20}BrNO_2$·HCl) C, H, Br, N.

2,3,4,5-Tetrahydro-3,6-dimethyl-1-phenyl-1*H*-3-benzazepine-7,8-diol Hydrobromide (34e). A solution of 160 mg (0.54 mmol) of **4d** in ethyl formate (20 mL, 18.3 g, 0.25 mol) was stored at 25 °C for 24 h. The solution was evaporated to dryness and the residue dissolved in ether; the ether solution was washed with 5% HCl, 5% $NaHCO_3$, and water. The dried ($MgSO_4$) ether solution was concentrated to give **26** ($R_1 = CH_3$, $R_2 = R_3 = H$) as an oil (130 mg, 74%): IR (film) 1675 (NCHO) cm^{-1}; NMR ($CDCl_3$) (many peaks doubled due to presence of two formyl isomers) δ 7.94, 7.91 (1, s, CHO), 7.18 (5, m, phenyl H), 6.37, 6.23 (1, s, 9 H), 4.29, 4.15 (1, m, 1-CH), 4–3.5 (m, CH_2NCOCH_2, OCH_3), 2.82 (2, m, 5-CH_2), 2.20, 1.80 (3, s, 6-CH_3). A solution of 3.5 g (0.011 mol) of this oil in 50 mL of THF and BH_3 (20 mL of 1 M) was stirred at 0 °C for 1 h and at 25 °C for 16 h; then 10 mL of 12 N HCl was added, and the solvent was removed under vacuum. The residue was dissolved in H_2O, made basic with NaOH, and extracted with Et_2O. The ether extract was treated with 50 mL of MeOH containing excess ethereal HCl and refluxed for 2 h. Evaporation of the solvents gave 2.7 g of a colorless solid, which was collected and converted to the free base with aqueous NaOH. The free base was dissolved in 100 mL of CH_2Cl_2; BBr_3 (7.95 g, 0.31 mol) was added, and the solution was stirred for 3.5 h. The volatiles were removed under vacuum, and the residue was dissolved in methanol. Concentration of the methanol gave a residue, which was recrystallized from H_2O to give 1.5 g (37%) of crystals, mp 168–170 °C. Anal. ($C_{18}H_{21}NO_2$·HBr·0.5H_2O) C, H, N.

6-Bromo-2,3,4,5-tetrahydro-7,8-dimethoxy-3-methyl-1-phenyl-1*H*-3-benzazepine Hydrochloride (33b). A solution of **27** free base (10 g, 0.028 mol) in 90% formic acid (44 mL) and 37% HCHO (6.0 mL, 0.084 mol) was heated on a steam bath for 4 h. The reaction mixture was poured into ice water, made basic with NaOH, and extracted wiith ether. Concentration under vacuum gave 9.14 g (86%) of a white solid, mp 108–110 °C. The hydrochloride salt prepared in ether melted at 220–221 °C. Anal. ($C_{19}H_{22}BrNO_2$·HCl) C, H, N.

2,3,4,5-Tetrahydro-1-(4-hydroxyphenyl)-6-iodo-1*H*-3-benzazepine-7,8-diol Hydrobromide (29l). A suspension of **4k** hydrobromide (7.8 g, 0.018 mol) in a mixture of 300 mL of CH_2Cl_2 and 30 mL of trifluoroacetic anhydride was stirred for 2 h, and then the solvents were removed undr vacuum. Toluene was added to the residue, and the solution was concentrated under vacuum to give 8.7 g (98%) of the *N*-trifluoroacetyl derivative. A solution of this in 60 mL of toluene was added to a solution of *n*-butyl

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lithium (25 mL of 2.6 M, 0.065 mol) in 200 mL of ether held at −78 °C. After 15 min a solution of I_2 (9.1 g, 0.036 mol) in 60 mL of ether was added in one portion, and the reaction mixture was allowed to warm to 25 °C. Addition of 200 mL of 10% HCl gave a solid that which was collected, dissolved in CH_2Cl_2 containing some MeOH, washed with saturated NaCl, dried over $MgSO_4$, and concentrated to dryness under vacuum. Recrystallization from a MeOH–EtOAc–Et_2O mixture gave 4.67 g (55%) of **28l** as crystals, mp 237–239 °C. Boron tribromide (11.9 g, 0.0476 mol) was added dropwise to a solution of **28l** (4.31 g, 0.0098 mol) in 300 mL of CH_2Cl_2 at 0 °C. After stirring for 4 h at 25 °C, 50 mL of MeOH was added and the solvents were removed under vacuum. The residue was recrystallized twice from water to give 2.1 g (44%) of **29l**: mp 240 °C dec; MS, *m/e* 397. Anal. ($C_{16}H_{16}INO_3$·HBr) C, H, N.

4-Hydroxy-3-methoxy-5-methyl-*N*,*N*-dimethylbenzylamine (22). *o*-Vanillin (228 g, 1.5 mol) was added to a solution of 60 g of NaOH in 1.5 L of H_2O. $NaBH_4$ (37.85 g, 1 mol) was slowly added to the resulting solution while keeping the temperature below 25 °C. After 0.5 h 10% H_2SO_4 was added to bring the pH to 5.5. Chilling gave 56.6 g of solid, and concentration of the filtrate and recrystallization of the residue from MeOH gave an additional 30.3 g (total 86.9 g, 86%) of product, which showed only one spot on TLC (10% MeOH–$CHCl_3$, SiO_2) and whose NMR spectrum was in agreement with that of 2-hydroxy-3-methoxybenzyl alcohol. A suspension of 30.8 g (0.2 mol) of this benzyl alcohol and 1.5 g of 10% Pd/C in 100 mL of 10% TFA in HOAc was shaken under 4 atm of H_2 at 100 °C for 7 h. Removal of the catalyst by filtration and concentration under vacuum gave an oil that was dissolved in Et_2O, and this solution was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated under vacuum. This gave an oil that crystallized on standing (23.5 g, 84%), which by TLC (10% MeOH–$CHCl_3$, SiO_2) showed only one component and whose NMR spectrum was consistent with that of 2-methoxy-6-methylphenol. A mixture of this phenol (6.94 g, 0.05 mol), 11.25 mL (0.1 mol) of 40% aqueous dimethylamine, and 5 mL (0.064 mol) of 37% aqueous formaldehyde was heated on a steam bath with good stirring for 3 h. Removal of the solvents under vacuum and addition of Et_2O to the residue gave a solid, which on recrystallization from ether gave 7.61 g (76%) of a solid, mp 97–98 °C. Anal. ($C_{11}H_{17}NO_2$) C, H, N.

(3,4-Dimethoxy-5-methylphenyl)acetonitrile (24). Iodomethane (52.4 g, 0.37 mol) was added to a solution of **22** (112 g, 0.57 mole) in 1 L of acetone giving a suspension in an exothermic reaction. After 10 min, KCN (39.8 g, 0.61 mol) was added and the suspension refluxed for 2 h. After the reaction mixture stood at room temperature for 18 h, it was diluted with water, extracted 3 times with ether, and the ether was washed in succession with H_2O, 10% NaOH, H_2O, 10% HCl, and H_2O. Concentration of the ether gave 45 g (68%) of an oil, which showed only trace impurities on TLC (5% MeOH–$CHCl_3$, SiO_2) and whose NMR spectrum agreed with that expected for **23**. A solution of **23** (45 g, 0.25 mol) in 0.75 L of acetone, 76 mL (101 g, 0.80 mol) of dimethyl sulfate, and K_2CO_3(91 g, 0.66 mol) was refluxed for 3 h, diluted with H_2O, and extracted with ether. The ether was washed with H_2O, dilute NH_4OH, and H_2O, dried over $MgSO_4$, and concentrated to give 38 g (79%) of an oil, which was futher purified by vacuum distillation, bp 120–125 °C (0.04 torr). IR and NMR spectra were consistent with those expected for **24**.

3,6-Dimethylveratrole (16). 3,6-Dimethylcatechol[35] (4.58 g, 0.0331 mol), 46 mL of 10% NaOH, and 13 mL of dimethyl sulfate were refluxed for a total of 1.5 h; 10 mL of 40% NaOH and 6 mL of dimethyl sulfate were added after 0.5 h of reflux, and 5 mL of 40% NaOH and 3 mL of dimethyl sulfate were added after 1 h of reflux. The cooled reaction mixture was extracted twice with Et_2O. The combined extracts were washed with H_2O, 10% NaOH, and H_2O, then dried over anhydrous $MgSO_4$ and concentrated to 4.78 g (87%) of amber liquid, which contained less than 1% of monomethylated product by VPC analysis and whose NMR spectrum was consistent with that expected for **16**.

Registry No. **1**, 67287-49-4; **2** (R = OCH_3), 6388-72-3; **2** (R = H), 96-09-3; **3** (R_6 = CH_3, R_9 = H, R = $OC(CH_3)_3$, R_4 = OCH_3), 104113-99-7; **3a**, 104129-98-8; **3b**, 67287-37-0; **3d**, 104113-86-2; **3f**, 62717-74-2; **3g**, 95413-95-9; **3h**, 71636-38-9; **3k**, 104133-97-5; **3m**, 78495-86-0; **3o**, 104114-04-7; **3p**, 104114-05-8; **3q**, 104114-06-9; **3r**, 104113-98-6; **4a**, 77969-31-4; **4b**, 67287-38-1; **4c**·HCl, 104113-78-2; **4d**, 71157-99-8; **4f**, 104113-87-3; **4g**, 72912-25-5; **4h**, 67287-53-0; **4k**·HBr, 104113-82-8; **4k** (trifluoroacetyl deriv.), 73894-45-8; **4m**, 77200-88-5; **4o**, 104114-07-0; **4p**, 104114-08-1; **4q**, 104114-09-2; **4r**, 104114-00-3; **5h**, 13005-14-1; **6h**, 74427-18-2; **6o**, 104114-01-4; **6p**, 104114-02-5; **6q**, 104114-03-6; **7**, 100-06-1; **8**, 637-69-4; **9**, 72912-33-5; **10**, 621-59-0; **11b**, 37687-57-3; **11c**, 2973-58-2; **12** (benzyl alcohol), 93983-13-2; **12** (benzyl chloride), 93983-14-3; **12b**, 5417-17-4; **12b** (5-chloro), 18268-68-3; **12b** (5-chloro, benzyl alcohol), 18268-78-5; **12b** (5-chloro, benzyl chloride), 104113-74-8; **12c**, 55171-60-3; **12c** (benzyl alcohol), 72912-38-0; **12c** (benzyl chloride), 7477-50-1; **13b**, 7537-07-7; **13b** (5-chloro), 104113-75-9; **13c**, 72912-39-1; **16**, 72912-16-4; **16** (diol), 2785-78-6; **18**, 148-53-8; **18** (alcohol), 4383-05-5; **19**, 2896-67-5; **22**, 104113-84-0; **23**, 104113-85-1; **24**, 92367-72-1; **25a**, 72912-24-4; **25c**, 72912-40-4; **25c**·HCl, 104113-73-7; **25d**, 77200-86-3; **25f**, 120-20-7; **25h**, 67287-36-9; **25k**, 72912-40-4; **25o**, 46274-23-1; **25p**, 75626-15-2; **25q**, 72912-19-7; **25r**, 46274-24-2; **25r**·HCl, 104113-76-0; **26c**, 104114-10-5; **26d**, 104114-11-6; **26e**·HCl, 78495-79-1; **26f**·HCl, 104113-77-1; **27**, 67287-41-6; **28**, 104113-83-9; **29a**, 77969-32-5; **29a**·HBr, 77969-26-7; **29b**, 71636-61-8; **29b**·HBr, 67287-39-2; **29c**, 71636-62-9; **29c**·HBr, 67287-42-7; **29d**, 104114-14-9; **29d**·HBr, 71158-00-4; **29e**, 77969-34-7; **29e**·HCl, 77969-35-8; **29f**, 102430-68-2; **29f**·HBr, 62717-75-3; **29g**, 102430-69-3; **29g**·HBr, 72912-26-6; **29h**·MS, 67227-57-0; **29h**·HBr, 67287-54-1; **29i**, 80751-71-9; **29i**·HBr, 67287-63-2; **29k**, 104114-15-0; **29k**·HBr, 67287-79-0; **29l**, 104129-99-9; **29l**·HBr, 104129-97-7; **29m**, 78495-91-7; **29m**·MS, 104113-88-4; **29n**, 104113-89-5; **29o**, 72912-37-9; **29o**·HBr, 72912-36-8; **29p**, 104114-17-2; **29p**·HBr, 104113-91-9; **29q**, 104114-18-3; **29q**·HBr, 104113-92-0; **29r**, 104114-16-1; **29r**·HBr, 104113-90-8; **30**, 93383-22-3; **30**·HCl, 72912-22-2; **32a**, 104114-19-4; **32a**·HCl, 72912-23-2; **32b**, 104114-20-7; **32b**·HCl, 104113-93-1; **32c**, 104114-21-8; **32c**·HCl, 72912-58-4; **33b**, 104113-80-6; **33b**·HCl, 104113-81-7; **33c**, 104114-12-7; **33d**, 104114-13-8; **33e**, 104113-79-3; **34a**, 74115-04-1; **34a**·HCl, 67287-59-6; **34b**, 104114-22-9; **34b**·HBr, 74114-95-7; **34c**, 104114-23-0; **34c**·HBr, 104113-94-2; **34d**, 104130-00-9; **34d**·HBr, 104113-95-3; **34e**, 78495-89-3; **34e**·HBr, 71157-98-7; **34f**, 104114-24-1; **34f**·HCl, 104113-96-4; 4-$H_3COC_6H_4CH(OH)CH_3$, 3319-15-1; 4-$H_3COC_6H_4CHBrCH_2Br$, 19484-05-0.

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