Synthesis, Renal Vasodilator and Dopamine-Sensitive Adenylate Cyclase Activities of *O*-Methyl Derivatives of 6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-benzazepin-7,8-diol (SK&F 82526)

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The three possible mono-*O*-methyl derivatives of 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-benzazepin-7,8-diol (SK&F 82526) (**1**) have been synthesized to facilitate the isolation and characterization of metabolites of this compound and for biological testing. The syntheses generally involved preparation of appropriately substituted benzaldehydes, conversion of these to phenylacetic acids and use of these to *N*-acylate arylethanolamines. The phenylacetamides thus formed were reduced to amines and these were deprotected and cyclized to the desired final products. In one case deprotection followed cyclization. These compounds were tested as activators of dopamine-sensitive adenylate cyclase (a measure of DA-1 agonist activity) and as renal vasodilators. All three *O*-methyl derivatives were much less potent than **1** in cyclase activation and as renal vasodilators. Weak inhibition of adenyl cyclase was also observed for all three compounds and one showed weak renal vasoconstrictor activity. Preliminary investigation of the metabolism of **1** disclosed that two of the three monomethoxy compounds were formed in trace amounts in the rat and the dog. In a related investigation, the trimethoxy derivative of **1** was subjected to acid-catalyzed hydrolysis conditions. The relative ease of cleavage of methoxy groups was 7 > > 4′ > 8.

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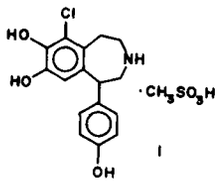
Introduction.

SK&F 82526-J, **1** [6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-benzazepin-7,8-diol methanesulfonate] is a potent and selective renal vasodilator with a postsynaptic (DA-1) dopaminergic mechanism of action which is currently undergoing clinical evaluation [1-3].



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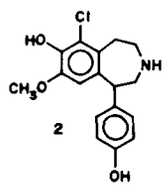
The synthesis of the three possible mono-*O*-methyl derivatives **2-4** of this compound was accomplished for pharmacological evaluation, to facilitate the isolation and characterization of metabolites of **1** and as analytical reference standards. Early work on the study of the metabolism of **1** in rats and dogs established that *O*-methylation was a significant but not primary route of transformation of this compound [4].



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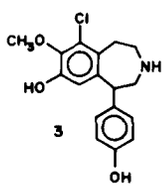

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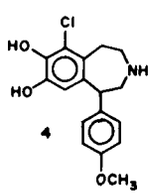

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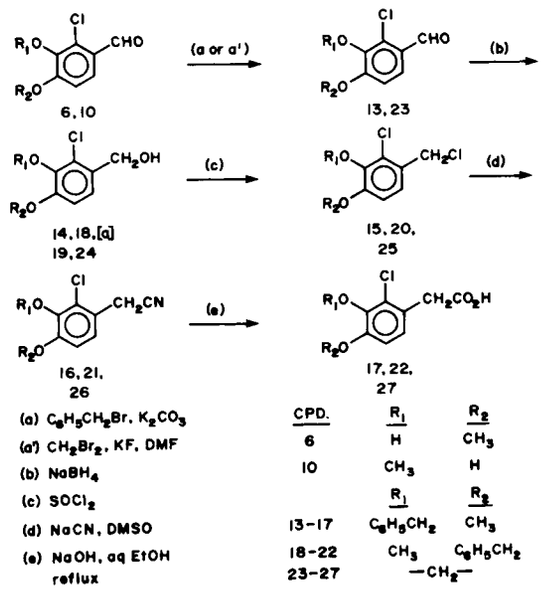
We also investigated the relative ease of acid-catalyzed hydrolytic cleavage of the three methoxyl groups present in the trimethyl ether (and synthetic precursor) of **1**, (*i.e.*, **41**). The relative ease of cleavage was 7 > > 4′ > 8.

Synthesis.

The synthetic approaches to the monomethoxy compounds **2-4** followed similar paths. Appropriately substituted protected phenylacetic acids were prepared (as shown in Scheme I and Table I), each converted to the

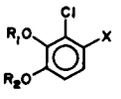
Scheme I Aldehydes, Benzyl Alcohols, Benzyl Chlorides, Phenylacetonitriles, Phenylacetic Acids



note: [a] In one case, synthesis of compounds **18** and **19**, the order of the *O*-benzylation and sodium borohydride steps was reversed.

Table I

Aldehydes, Benzyl Alcohols, Benzyl Chlorides, Phenylacetonitriles and Phenylacetic Acids

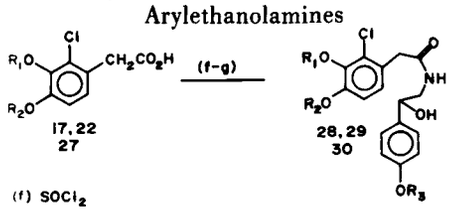


Compound	R_1	R_2	X	procedure [a]	mp, °	Yield, %
13	$C_6H_5CH_2$	CH_3	CHO	A	86-87	83
14	$C_6H_5CH_2$	CH_3	CH_2OH	B	55-57	67
15	$C_2H_5CH_2$	CH_3	CH_2Cl	C	58-61	92
16	$C_6H_5CH_2$	CH_3	CH_2CN	D	55-55.5	57
17	$C_6H_5CH_2$	CH_3	CH_2CO_2H	E	126-128	79
18	CH_3	H	CH_2OH	B	78-79	89
19	CH_3	$C_6H_5CH_2$	CH_2OH	A	oil [b]	60
20	CH_3	$C_6H_5CH_2$	CH_2Cl	C	oil [c]	~100
21	CH_3	$C_6H_5CH_2$	CH_2CN	D	101-102	69
22	CH_3	$C_6H_5CH_2$	CH_2CO_2H	E	133.5-135.5	82
23	$--CH_2--$		CHO	F	122-123	47
24	$--CH_2--$		CH_2OH	B	104-106	86
25	$--CH_2--$		CH_2Cl	C	94-96	89
26	$--CH_2--$		CH_2CH	D	130-131.5	98
27	$--CH_2--$		CH_2CO_2H	E	171.5-172.5	86

[a] The letter designation for "procedure" has been used to link the tables with Schemes I-III and with the Experimental. [b] bp (0.8 torr) 187-189°. [c] bp (1.0 torr) 195 ±5°.

acid chloride and this used to acylate a 4-alkoxyphenylethanolamine (Scheme II, Table II). The resulting amides were reduced (borane) and the aminoalcohols produced were either deprotected and cyclized to the final products or cyclized and then deprotected (Scheme III, Table III). Cyclization conditions in two cases (**2** and **4**) were similar to those used in the preparation of **1** [sulfuric acid in trifluoroacetic acid (TFA)] though yields were lower (Scheme III, Table IV). The 7-methoxy analogue **3** required a stronger acid, trifluoromethanesulfonic acid in TFA, to accomplish ring closure. Thus free phenolic hydroxyls do not preclude the desired cyclization from occurring though side-reactions are evidently more prevalent.

Scheme II Synthesis of Phenylacetamides from Arylethanolamines



(f) $SOCl_2$

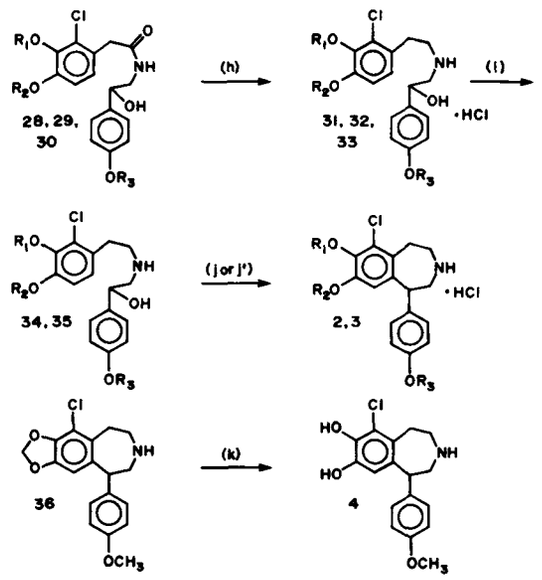
(g) $H_2NCH_2CHOHC_6H_4$-4-OR_3, base

CPD.	R_1	R_2
17, 28 [a]	$C_6H_5CH_2$	CH_3
22, 29 [a]	CH_3	$C_6H_5CH_2$
27, 30 [b]	$-CH_2-$	

notes: [a]. R_3 = $C_6H_5CH_2$

[b]. R_3 = CH_3

Scheme III Synthesis of Aminoalcohols and Cyclization to 3-Benzazepines (Deprotection)



(h) BH_3, THF; CH_3OH, HCl

(i) H_2, Pd-C

(j) H_2SO_4, CF_3CO_2H

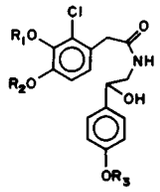
(j') CF_3SO_3H, CF_3CO_2H

(k) BCl_3

CPD.	R_1	R_2	R_3
28, 31	$C_6H_5CH_2$	CH_3	$C_6H_5CH_2$
29, 32	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$
30, 33	$-CH_2-$		CH_3
	R_1	R_2	R_3
34	H	CH_3	H
35	CH_3	H	H

Table II

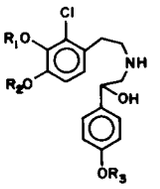
Phenylacetamides



Compound	R_1	R_2	R_3	procedure	mp, °	yield, %
28	$C_6H_5CH_2$	CH_3	$C_6H_5CH_2$	G	143-144	61
29	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	G	135-136	61
30	--CH_2--		CH_3	G	130.5-132.5	77

Table III

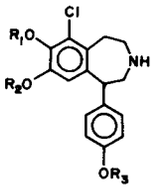
Amino Alcohols, Protected and Deprotected



Compound	R_1	R_2	R_3	procedure	mp, °	yield, %
31	$C_6H_5CH_2$	CH_3	$C_6H_5CH_2$	H	165-166	82
32	CH_3	$C_6H_5CH_2$	$C_6H_5CH_2$	H	166-167	77
33	--CH_2--		CH_3	H	169-171	65
34	H	CH_3	H	I	foam	77
35	CH_3	H	H	I	foam	85

Table IV

3-Benzazepines, Protected and Deprotected

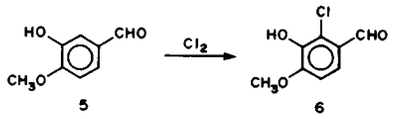


Compound	R_1	R_2	R_3	procedure	mp, °	yield, %
2	H	CH_3	H	J, H_2SO_4, TFA	296 (dec)	54
3	CH_3	H	H	J, CF_3SO_3H, TFA	290-294 (dec)	37
36	--CH_2--		CH_3	J, H_2SO_4, TFA	244-246	41
4	H	H	CH_3	K, BCl_3 [a]	267-271 (dec)	81

[a] The methylenedioxy-3-benzazepine was treated with boron trichloride in dichloromethane to form the 7,8-dihydroxy compound (Procedure K).

Preparation of Required Vanillin Derivatives.

Appropriately substituted vanillin derivatives formed the key intermediates in the synthetic schemes for all three target compounds. The synthetic route to the 8-methoxy compound **2** began with isovanillin (**5**) which was 2-chlorinated to give **6** by a known procedure [5].



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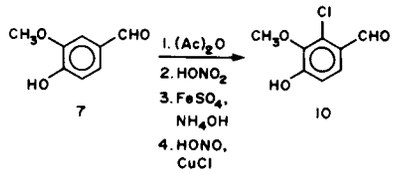
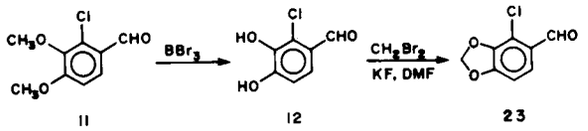
To prepare the 7-methoxy compound **3** we required 2-chlorovanillin (**10**) obtained from vanillin (**7**) as follows [6]:



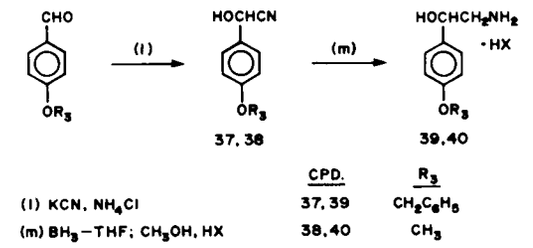
The 4'-methoxy compound **4** was prepared starting with 2-chloroveratraldehyde **11**. This was demethylated to **12** for introduction of the methylenedioxy group to give **21** [7].



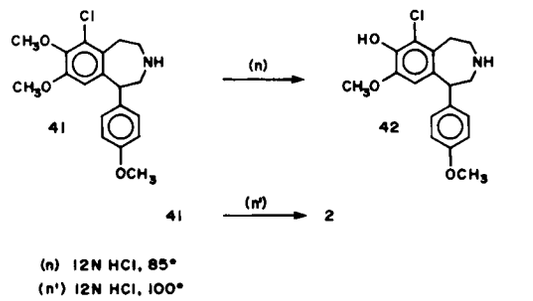
The ensuing steps for all three sequences are shown in Schemes I-III and Tables I-IV.

The alkoxyphenylethanolamines required as intermediates were prepared by cyanohydrin reactions on alkoxybenzaldehydes followed by borane reduction (see Scheme IV). In the 4-benzyloxy case **20a** destruction of the borane-product complex by hydrochloric acid in methanol in one attempt caused substantial formation of the β-methoxy derivative of the product by acid-catalyzed exchange [8].

Scheme IV Arylethanolamines



Scheme V Hydrolytic Demethylations



Demethylation Studies.

Aqueous hydrochloric acid (12*N*) showed significant selectivity in the demethylation of the trimethoxybenzazepine **41** (see Scheme V). A four hour treatment of **41** at 85° in this system resulted in isolation of the 7-hydroxy-8,4'-dimethoxy compound **42** (7-methoxyl cleavage) while treatment of **41** for 13 hours at 100° gave the 7,4'-dihydroxy-8-methoxy compound **2** (7,4'-dimethoxy cleavage). The fully-cleaved product **1** was present in the reaction mixture of the latter experiment, but further treatment under the same conditions produced increasing amounts of resinous by-products while still leaving partly methylated compounds, primarily **2**.

Table V

Renal Vasodilator [a] and Adenylate Cyclase [b] Data

Compound	Renal vasodilator activity, ED_{15} μg/kg, i. v.	Dopamine-sensitive adenylate cyclase activation EC_{50},M	inhibition IC_{50},M
2	[c]	None to 10^{-4}	1×10^{-5} (30)
3	44(27) [d]	$\sim 1 \times 10^{-6}$ (30 [e]	$> 1 \times 10^{-5}$ (30)
4	73(36)	1.5×10^{-7} (50)	$> 1 \times 10^{-5}$ (50)
1	0.3(59)	1.8×10^{-8} (90)	–
Dopamine	3.5(43)	3.5×10^{-6} (100)	

[a] Renal vasodilator activity was determined in anesthetized dogs according to the method described by Hahn *et al.* [2]. [b] Dopamine-sensitive adenylate cyclase activity was determined in rat caudate homogenates according to the methods of Kebabian *et al.* [15], Carenzi *et al.* [16] and Guidotti *et al.* [17]. [c] This compound displayed renal vasoconstrictor activity at infusion rates of 3, 30 and 300 μg/kg/minute reaching a maximum of 15% decreased renal blood flow at 30 μg/kg/minute. [d] Figure in parenthesis represents the maximum observed percentage increase in renal blood flow. [e] Number in parenthesis is the maximal stimulation expressed as % of maximal response to dopamine.

Pharmacology, Biochemistry and Metabolism.

None of three monomethoxy compounds **2-4** showed potent or effective renal vasodilator activity (see Table V). The analog which retains the intact catechol moiety **4** showed the maximum activity but even this was only of a modest nature compared to **1**. The 8-monomethoxy analog **2** caused renal vasoconstruction at all infusion rates tested.

Dopamine-sensitive adenyl cyclase testing produced results similar to that of renal vasodilator testing. The 8-monomethoxy analog **2** was inactive in activation testing and **3** showed very weak activity while **4** showed partial agonist activity with an EC_{50} of .15 μM but had a maximal stimulation of only 50% of that of dopamine (Table V). When tested as inhibitors of the natural activator dopamine in this system all three compounds **2-4** showed weak inhibitory activity [9].

Preliminary study of the metabolism of **1** in rats and dogs has indicated that the monomethoxy compounds **2** and **3** are formed in minor amounts [4]. No evidence for the formation of **4** was found.

EXPERIMENTAL

Melting points below 200° were determined on a Thomas-Hoover apparatus; melting points above 200° were determined in capillary tubes in a heated block (Mel Temp). All are uncorrected. Elemental analyses and mass spectra were determined by members of the Analytical, Physical and Structural Chemistry Department of Smith Kline & French Laboratories. The ir spectra of solids were determined as *ca* 1% dispersions in potassium bromide discs while liquids were cast as neat films on potassium bromide plates and spectra measured on a Perkin Elmer Model 735 IR spectrophotometer. The ^{1}H-nmr spectra were determined on a Varian T-60 60 MHz spectrometer. Fourier-transform (ft) derived spectra, both ^{1}H and ^{13}C, were measured on a Varian FT 80A instrument. Gc was performed on a Perkin-Elmer Model 3920 gas chromatograph, equipped with a flame ionization detector, using; A (4 ft - 10% OV-225 [glass, 4 mm I. D. on Gas Chrom WHP, 100-120 mesh]) or; B (3 ft - 3% OV-101 [glass, 1.8 mm I. D. on Gas Chrom WHP, 80-100 mesh]. Tlc was performed on precoated silica plates (250 μ, Analtech) using chloroform-methanol as specified. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E spectrometer at 70 eV. Uv spectra were obtained on a Cary 219 spectrophotometer.

Chemistry.

2-Chloro-3-hydroxy-4-methoxybenzaldehyde (**6**) [5].

A slurry of isovanillin (**5**) (200 g, 1.33 moles) was stirred in 3 ℓ of dichloromethane and cooled to -60°. Gaseous chlorine (103 g, 1.45 moles) was bubbled in over a period of 20 minutes. The mixture was allowed to warm slowly to -20 to -25° and maintained there for 6 hours, then was allowed to warm to ambient temperature and was stirred overnight. The mixture was cooled to -10°, filtered, and the solid was washed with cold dichloromethane. Recrystallization from acetonitrile gave 174.7 g (71%), mp 203-205° (lit [5] 205-206°); ir 1662, 1280, 1035 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 3.97 (s, 3, OCH_3), 6.98 (d, 1, J_{AB} = 9 Hz, Ar*H*), 7.39 (d, 1, J_{AB} = 9 Hz, Ar*H*), 10.12 (s, 1, C*H*O); gc (A), 140-220° at 16° min^{-1}, single component.

2-Chloro-4-methoxy-3-(phenylmethoxy)benzaldehyde (**13**) (Procedure A).

Into 400 ml of dimethylformamide was added **6** (40.0 g, 0.27 mole) and powdered potassium carbonate (41.5 g, 0.30 mole). To this stirred mixture was added dropwise benzyl bromide (35.7 ml, 0.30 mole). The mixture was stirred for 36 hours at ambient temperature, diluted with water (1.5 ℓ) and the solid which formed was filtered and washed with water. Recrystallization from *n*-butyl chloride-hexane gave 61.5 g (83%) of **13**, mp 86-87°; ir: 1668, 1580, 1238, 941 cm^{-1}; nmr (deuteriochloroform): 3.97 (s, 3, OCH_3), 5.05 (s, 2, ArCH_2), 6.92 (d, 1, J_{AB} = 9 Hz, Ar*H*), 7.21-7.61 (m, 5, Ar*H*), 7.39 (d, 1, J_{AB} = 9 Hz, Ar*H*).

Anal. Calcd. for $C_{15}H_{13}ClO_3$: C, 65.11; H, 4.74. Found: C, 64.79; H, 4.81.

2-Chloro-4-methoxy-3-(phenylmethoxy)benzenemethanol (**14**) (Procedure B).

A 61.3 g (0.222 mole) quantity of **13** was dissolved in 2-propanol (300 ml) to which was added a slurry of sodium borohydride (4.8 g, 0.12 mole) in 2-propanol (50 ml). The mixture was heated to 70° for 1 hour, then cooled to ambient temperature. A gum formed. The addition of 10% hydrochloric acid gave a clear solution, and stirring was continued overnight. The solution was extracted with dichloromethane. This solution was dried (magnesium sulfate) and concentrated under vacuum to afford a dark oil. Trituration with methanol gave light yellow crystals, 10.6 g, mp 92-92.5° and an additional 3.84 g by dilution of the filtrate with water (identical by tlc: chloroform R_f 0.40). The ir spectrum of this unknown yellow crystalline material showed lack of a hydroxyl absorption. White needles, 3.60 g, mp 55-57° were also obtained as a second crop from aqueous methanol. These white crystals were analytically pure **14**. The filtrate was concentrated to an oil, 38.0 g; tlc, chloroform: oil, R_f 0.20 (major), traces 0.30, 0.50; **13**, 0.55; crystalline **14**, R_f 0.20; ir 3200, 1596, 1490, 1295, 1283, 1042 cm^{-1}; nmr (deuteriochloroform): 3.82 (s, 3, OCH_3), 4.61 (s, 2, CH_2OH), 5.00 (s, 2, ArCH_2), 6.70-7.65 (m, 7, Ar*H*).

Anal. Calcd. for $C_{15}H_{15}ClO_2$: C, 64.64; H, 5.42. Found: C, 64.43; H, 5.63.

2-Chloro-1-(chloromethyl)-4-methoy-3-(phenylmethoxy)benzene (**15**) (Procedure C).

Both oil and crystalline **14** (40.0 g, 143 mmoles) were dissolved in dichloromethane (300 ml) to which was added thionyl chloride (23.8 g, 200 mmoles). The solution was refluxed for 1.5 hours. The solvents were removed under vacuum; toluene added and removed under vacuum to give an oil. A small portion was distilled (bp 207° at 5.0 torr). Distillation resulted in considerable decomposition. The distilled oil crystallized, mp 58-61°. Seeding of the undistilled oil gave a waxy solid, 38.95 g (92%), mp 45-50°; ir (film): 2900, 1590, 1495, 1279, 1042, 700 cm^{-1}; nmr (deuteriochloroform): 3.80 (s, 3, OCH_3), 4.61 (s, 2, CH_2Cl), 5.00 (s, 2, ArCH_2), 6.62-7.70 (m, 7, Ar*H*).

Anal. Calcd. for $C_{15}H_{14}Cl_2O_2$: C, 60.62; H, 4.75; Cl, 23.86. Found: C, 60.61; H, 4.69; Cl, 23.67.

2-Chloro-4-methoxy-3-(phenylmethoxy)benzeneacetonitrile (**16**) (Procedure D).

Into dimethylsulfoxide (200 ml) was added **15** (42.2 g, 142 mmoles) and finely ground sodium cyanide (10.5 g, 214 mmoles). The exotherm which occurred was moderated with an ice bath. The mixture was stirred at ambient temperature for 3 hours. The mixture was diluted with water (1.5 ℓ) and extracted with ether. The ether solution was dried (sodium sulfate) and concentrated under vacuum to give 43 g of a dark oil. The oil was distilled (bp 180-195° at 0.4 torr) to give 26.26 g which crystallized. Recrystallization from *n*-butyl chloride-hexane gave 23.45 g (57%) mp 55-55.5°; ir: 2345, 1595, 1490, 1290, 1050 cm^{-1}; nmr (deuteriochloroform): 3.72 (s, 2, CH_2CN), 3.82 (s, 3, OCH_3), 5.02 (s, 2, ArCH_2), 6.75-7.60 (m, 7, Ar*H*).

Anal. Calcd. for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87. Found: C, 66.74; H, 4.94; N, 4.67.

2-Chloro-4-methoxy-3-(phenylmethoxy)benzeneacetic Acid (**17**) (Procedure E).

To a mixture of ethanol (45 ml) and 20.2 ml of 25% aqueous sodium hydroxide (160 mmoles) was added **16** (23.3 g, 80 mmoles). The mixture was refluxed overnight. The majority of the ethanol was removed under vacuum and the solution was diluted with water and extracted with ether. The aqueous solution was acidified with 12*N* hydrochloric acid. Crystals formed; these were filtered and washed with water. Recrystallization from *n*-butyl chloride gave 18.28 g (79%), mp 126-128°; ir: 1690, 1600, 1490, 1275, 1040 cm^{-1}; nmr (deuteriochloroform): 3.70 (s, 2, CH_2CO$_2$H), 3.80 (s, 3, OCH_3), 5.00 (s, 2, ArCH_2), 6.80 (d, 1, J_{AB} = 9 Hz, Ar*H*), 7.08 (d, 1, J_{AB} = 9 Hz, Ar*H*), 7.16-7.70 (m, 5, Ar*H*), 10.55 (br s, 1, CO$_2$*H*).

Anal. Calcd. for $C_{16}H_{15}ClO_4 \cdot 1/8\ H_2O$: C, 61.74; H, 4.94. Found: C, 62.05; H, 5.07.

2-Chloro-*N*-[2-hydroxy-2-[4-(phenylmethoxy)phenyl]ethyl]-4-methoxy-3-(phenylmethoxy)benzeneacetamide (**28**) (Procedure G).

To dichloromethane (35 ml) was added **17** (2.0 g, 6.62 mmoles) and thionyl chloride (1.19 g, 10 mmoles). The solution was refluxed for 2.5 hours. The solvents were removed under vacuum; toluene was added and removed under vacuum to give a residual oil; ir (film): 1795 cm^{-1}. Into a mixture of water (200 ml) and toluene (100 ml) was added potassium carbonate (2.42 g, 17.5 mmoles) and **39** (1.91 g, 6.85 mmoles). To this stirred mixture was added a solution of the acid chloride of **17** in 50 ml dichloromethane. The mixture was stirred vigorously for 1 hour, and the solid which formed was filtered and washed with toluene and water. Recrystallization from *n*-butyl chloride gave 2.1 g (61%), mp 143-144°; ir 3300, 1630, 1485, 1040, 750 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 3.30-3.80 (br m, 2, NHCH_2CHOH), 3.65 (s, 2, CH_2CO), 3.90 (s, 3, OCH_3), 4.60 (br s, 1, C*H*OH), 5.05 (s, 4, ArCH_2), 6.80-7.70 (m, 16, Ar*H*); ms: m/z 531 (M$^+$), 513, 226, 92 (100).

Anal. Calcd. for $C_{31}H_{30}ClNO_2 \cdot 1/8\ H_2O$: C, 69.69; H, 5.75; N, 2.62. Found: C, 69.41; H, 5.60; N, 2.76.

α-[[[2-[2-Chloro-4-methoxy-3-(phenylmethoxy)phenyl]ethyl]amino]methyl]-4-(phenylmethoxy)benzenemethanol Hydrochloride (**31**) (Procedure H).

A 23.58 g (44.3 mmoles) quantity of **28** was added to dry tetrahydrofuran (150 ml) and the mixture stirred. A 1.03 *M* solution of borane/tetrahydrofuran (85.3 ml, 88 mmoles) was added dropwise. The mixture became homogeneous. The solution was refluxed for 1.5 hours and cooled; methanol (200 ml) was added dropwise and the solution was refluxed for 2.0 hours. The solvents were removed under a stream of nitrogen, and the oil was diluted with ether. Ethereal hydrogen chloride was added, and the solid which formed was filtered to give 20.08 g (82%), mp 158-160°. A small portion was recrystallized from absolute ethanol, mp 165-166°. Both crystalline portions were identical by tlc, (9:1 v/v chloroform-methanol) R_f 0.40; ir: 1601, 1510, 1490, 1240, 1050, 830, 698 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 3.20 (br s, 6, $CH_2CH_2NHCH_2$), 3.85 (s, 3, OCH_3), 4.98 (s, 2, $ArCH_2$), 5.10 (s, 2, $ArCH_2$), 5.95 (br m, 1, CHOH), 6.80-7.15 (m, 2, ArH), 7.15-7.60 (m, 14, ArH).

Anal. Calcd. for $C_{31}H_{32}ClNO_4 \cdot HCl$: C, 67.15; H, 6.00; N, 2.53. Found: C, 67.04; H, 5.93; N, 2.61.

α-[[[2-(2-Chloro-3-hydroxy-4-methoxyphenyl)ethyl]amino]methyl]-4-hydroxybenzenemethanol Hydrochloride (**34**) (Procedure I).

Following the method of Kaiser [12], **31** (1.0 g, 1.8 mmoles) was hydrogenolyzed using 250 mg of 10% palladium on carbon in a mixture of 25 ml of ethanol and 25 ml of methanol to give a foam, 520 mg (77%), tlc [70:30 (v/v) chloroform-methanol] R_f 0.60 (major); 0.65, 0.40, 0.35, 0.30 all traces; nmr (deuteriochloroform-DMSO-d_6): 3.00-3.18 (brs, 6, $CH_2CH_2NHCH_2$), 3.85 (s, 3, OCH_3), 4.95-5.10 (m, 1, CHOH), 6.70-7.60 (m, 6, ArH); ms: m/z (no M^+), 284, 264, 262, 148.

Acid Cyclized Preparation of 6-Chloro-2,3,4,5-tetrahydro-7-hydroxy-1-(4-hydroxyphenyl)-8-methoxy-1*H*-3-benzazepine Hydrochloride (**2**) (Procedure J).

Crude **34** (11.0 g, 29.4 mmoles) was dissolved in 110 ml of trifluoroacetic acid. To this solution was added concentrated sulfuric acid (4.32 g, 44 mmoles). The mixture was refluxed for 15 minutes. Some crystalline material precipitated from solution. The majority of the trifluoroacetic acid was removed under a stream of nitrogen with warming, and the residual oil was diluted with ice/water, and made basic with 15*N* ammonium hydroxide. The solid which formed was dissolved in methanol and the solution was saturated with hydrogen chloride gas. The solution was concentrated to *ca* 150 ml, and crystals formed. Dilution with ether gave 6.1 g. A second crop, 1.28 g, was recrystallized from methanol-acetonitrile to give 760 mg, identical by tlc with the first crop material. Both crops were combined and recrystallized from methanol-acetonitrile to give tan crystals, 5.6 g (54%), mp 296° dec; ir: 2925, 1610, 1500, 1235, 840 cm^{-1}; uv (ethanol): λ max (log ε) 282 nm (3.60), 228 s (4.24), 208 (4.67); (methanol): 283 (3.54), 227 s (4.14), 206 (4.57); ^1H ft nmr (DMSO-d_6): 2.70-3.80 (m, 6, $CH_2CH_2NHCH_2$), 3.50 (s, 3, OCH_3), 4.58 (m, 1, ArCHAr), 6.20 (s, 1, ArH), 6.75 (d, 2, J_{AB} = 8 Hz, ArH), 6.98 (d, 2, J_{AB} = 8 Hz, ArH); ^{13}C ft nmr (DMSO-d_6): 26.57 (C_8), 44.50 (C_4), 44.76 (C_2), 49.62 (C_1), 56.16 (OCH_3), 111.65 (C_7), 116.02 ($C_{3'}$, $C_{5'}$), 120.96 (C_6), 128.68 ($C_{2'}$, $C_{6'}$), 129.39 (C_{5a} or C_{9a}), 130.64 ($C_{1'}$), 134.15 (C_{5a} or C_{9a}), 141.72 (C_7), 146.58 (C_8), 156.60 (C_4); ms: m/z 319 (M^+), 283 (100), 277, 212, 199, 107.

Anal. Calcd. for $C_{17}H_{18}ClNO_3 \cdot HCl$: C, 57.32; H, 5.38; N, 3.93. Found: C, 57.12; H, 5.58; N, 4.21.

4-Hydroxy-3-methoxy-2-nitrobenzaldehyde (**8**).

Vanillin **7** (200 g, 1.32 moles) was *O*-acetylated with acetic anhydride, 147 g (1.44 moles) in water [11] containing sodium hydroxide (54 g, 1.35 moles) to give 4-acetoxy-3-methoxybenzaldehyde, 173.2 g (68%), mp 75-76° (lit [6] mp 76-77°). This was added slowly to 830 ml of fuming nitric acid at -20°, the reaction mixture quenched on ice, the yellow precipitate stirred with water and made basic and kept at *p*H 10 (sodium hydroxide). The solution was filtered and the filtrate acidified to give **8** as a yellow crystalline solid, 142.4 g (81%) mp 133-134.5° (lit [6] mp 137°); ir: 3250, 1675, 1600, 1540, 1338, 1280 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 2.60 (br s, 1, OH), 3.90 (s, 3, OCH_3), 7.18 (d, 1, J_{AB} = 9 Hz, ArH), 7.58 (d, 1, J_{AB} = 9 Hz, ArH).

2-Amino-4-hydroxy-3-methoxybenzaldehyde (**9**).

A mixture of **8** (5.0 g, 25.9 mmoles), ferrous sulfate (67 g, 0.24 mole), 12*N* hydrochloric acid (0.42 ml) and water (150 ml) was stirred and heated at 90° and 25 ml of 15*N* ammonium hydroxide was added followed by two 10 ml portions of 15*N* ammonium hydroxide at 2 minute intervals [10]. The mixture was filtered hot, and adjusted to neutral *p*H with 15*N* ammonium hydroxide. Red crystals formed, and these were filtered to give 2.12 g, mp 126-127° (lit [11] mp 128-129°). The aqueous solution was extracted with dichloromethane (3 x 100 ml). The dichloromethane solution was dried (sodium sulfate) and concentrated to give 1.2 g, mp 121-123.5°. Both crystalline portions were identical by tlc (chloroform R_f 0.10) and were combined to give 3.32 g (79%); ir: 3400, 3300, 1635, 1615, 1200 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 3.81 (s, 3, OCH_3), 6.40 (d, 1, J_{AB} = 9 Hz, ArH), 7.18 (d, 1, J_{AB} = 9 Hz, ArH), 9.55 (br s, 1H, CHO).

2-Chloro-4-hydroxy-3-methoxybenzaldehyde (**10**).

Following the procedure of Raiford [11], **9** (2.90 g, 1.74 mmoles) was dissolved in 12*N* hydrochloric acid (4 ml) and diluted with water (2 ml), and cooled to 0°. Sodium nitrite (1.30 g) was added portionwise, followed by 2.0 *g of cuprous chloride* dissolved in 12*N* hydrochloric acid (10 ml). The temperature was maintained below 5° for the first 25% of the addition, then the remainder of the cuprous chloride solution was added rapidly and the mixture was then heated on a steam bath for 1 hour. Cooling and filtration gave **10**, 2.80 g (86%), mp 125-126.5° (lit mp 128-129°); ir 1660, 1575, 1500, 1225, 1040, 800 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 3.95 (s, 3, OCH_3), 6.95 (d, 1, J_{AB} = 11 Hz, ArH), 7.60 (d, 1, J_{AB} = 11 Hz, ArH), 10.18 (s, 1, CHO).

2-Chloro-4-hydroxy-3-methoxybenzenemethanol (**18**).

Procedure B was used to prepare **18** from **10** (17.6 g, 105 mmoles) as off-white crystals from *n*-butyl chloride, 15.76 g, (89%), mp 78-79°, with softening at 74°; ir: 3325, 1590, 1510, 1300, 1000 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 3.80 (s, 3, OCH_3), 4.60 (br s, 2, CH_2OH), 6.78 (d, 1, J_{AB} = 9 Hz, ArH), 7.60 (d, 1, J_{AB} = 4.5 Hz, ArH), 8.18 (br s, 1, OH).

Anal. Calcd. for $C_8H_{10}ClO_3$: C, 50.95; H, 4.81. Found: C, 51.32; H, 5.01.

2-Chloro-3-methoxy-4-(phenylmethoxy)benzenemethanol (**19**).

To a mixture of powdered potassium carbonate (14.4 g, 109 mmoles) and **18** (17.9 g, 95 mmoles) was added dimethylformamide (80 ml), and benzyl bromide (17.8 g, 104 mmoles) (see Procedure A). The mixture was diluted with water (*ca* 600 ml) and extracted with ether. The ether solution was washed with brine, dried (magnesium sulfate), filtered and concentrated under vacuum to a reddish oil, 26.0 g. This gave 17.07 g (60%) of a yellow-orange oil after distillation (bp 187-189° at 0.8 torr). The oil from a previous 5.3 mmole scale reaction was added prior to distillation; ir (film): 3300, 1595, 1490, 1270, 1015 cm^{-1}; nmr (deuteriochloroform): 2.30 (s, 1, OH), 3.90 (s, 3, OCH_3), 4.60 (s, 2, CH_2OH), 5.05 (s, 2, $ArCH_2$), 6.78 (d, 1, J_{AB} = 9 Hz, ArH), 7.02 (d, 1, J_{AB} = 9 Hz, ArH), 7.30 (br s, 5, ArH); gc (B) 100-250° at 16° min^{-1}, 99% purity.

Anal. Calcd. for $C_{15}H_{15}ClO_3$: C, 64.64; H, 5.42. Found: C, 64.37; H, 5.52.

2-Chloro-1-(chloromethyl)-3-methoxy-4-(phenylmethoxy)benzene (**20**).

Dichloromethane (100 ml) was added to **19** (16.88 g, 60.5 mmoles) and to this was added thionyl chloride (10.9 g, 91 mmoles). Procedure C was used to give a light yellow-green oil, 18.0 g (100%). A small portion was distilled to give an analytical sample (bp 195 ±5° at 1.0 torr). Distillation was accompanied by extensive decomposition; ir (film): 2900, 1590, 1410, 1280, 1040, 1025 cm^{-1}; nmr (deuteriochloroform): 3.80 (s, 3, OCH_3), 4.60 (s, 2, CH_2Cl), 5.05 (s, 2, $ArCH_2$), 6.78 (d, 1, J_{AB} = 9 Hz, ArH), 7.10 (d, 1, J_{AB} = 9 Hz, ArH), 7.30 (br s, 5, ArH).

Anal. Calcd. for $C_{15}H_{14}Cl_2O_2$: C, 60.62; H, 4.75; Cl, 23.86. Found: C, 60.37; H, 5.08; Cl, 23.67.

2-Chloro-3-methoxy-4-(phenylmethoxy)benzeneacetonitrile (**21**).

Crude **20**, 17.7 g (59.5 mmoles) was treated by Procedure D to give 15.0 g of product, mp 96-97.5°. Recrystallization from *n*-butyl chloride gave 9.52 g, mp 101-102° and a later crop, 1.50 g, mp 98-100°. Both

crops were combined to give 11.02 g (64%); ir: 2900, 2225, 1595, 1290, 1265, 1255, 1010 cm^{-1}; nmr (deuteriochloroform): 3.75 (s, 2, CH_2CN), 3.90 (s, 3, OCH_3), 5.10 (s, 2, $ArCH_2$), 6.82 (d, 1, J_{AB} = 9 Hz, Ar*H*), 7.18 (d, 1, J_{AB} = 9 Hz, Ar*H*), 7.40 (br s, 5, Ar*H*).

Anal. Calcd. for $C_{16}H_{14}ClNO_2$: C, 66.79; H, 4.90; N, 4.87. Found: C, 66.91; H, 5.07; N, 4.76.

2-Chloro-3-methoxy-4-(phenylmethoxy)benzeneacetic Acid (**22**).

A 10.22 g (35.4 mmoles) quantity of **21** was treated by Procedure E to give 10.15 g of **22**, mp 132-134°. Recrystallization from *n*-butyl chloride gave two crops, 8.92 g (87%), mp 133.5-135.5°. An analytical sample (from *n*-butyl chloride) had mp 129-131° as a partial hydrate; ir: 1718, 1595, 1488, 1220, 1040, 1030 cm^{-1}; nmr (deuteriochloroform): 3.72 (s, 2, C*H*, CO_2H), 3.90 (s, 3, OCH_3), 5.10 (s, 2, $ArCH_2$), 6.70 (d, 1, J_{AB} = 9 Hz, Ar*H*), 6.95 (d, 1, J_{AB} = 9 Hz, Ar*H*), 7.40 (s, 5, Ar*H*).

Anal. Calcd. for $C_{16}H_{15}ClO_4 \cdot 1/8\ H_2O$: C, 62.19; H, 4.96. Found: C, 62.21; H, 4.96.

2-Chloro-*N*-[2-hydroxy-2-(4-(phenylmethoxy)phenyl]ethyl]-3-methoxy-4-phenylmethoxy)benzeneacetamide **29**.

A 2.0 g (6.52 mmoles) sample of **22** was treated by Procedure G to give 2.70 g of **29** (78%), mp 139-142°. Recrystallization from *n*-butyl chloride gave 2.10 g (61%), mp 143-144°, (partial hydrate). An anhydrous sample, for elemental analysis, had mp 135-136°; ir: 3275, 1635, 1490, 1230, 1040 cm^{-1}; nmr (deuteriochloroform): 3.20-3.75 (m, 2, CH_2CHOH), 3.58 (s, 2, CH_2CO), 3.88 (s, 3, OCH_3), 4.70 (m, 1, C*H*OH), 5.01 (s, 2, $ArCH_2$), 5.10 (s, 2, $ArCH_2$), 6.65-7.6 (complex overlapping s, d, m, 16, Ar*H*).

Anal. Calcd. for $C_{31}H_{30}ClNO_5$: C, 69.98; H, 5.68; N, 2.63. Found: C, 70.09; H, 5.75; N, 2.75.

α-[[[2-[2-Chloro-3-methoxy-4-(phenylmethoxy)phenyl]ethyl]amino]ethyl]-4-(phenylmethoxy)benzenemethanol Hydrochloride (**32**).

Procedure H was used to convert 11.08 g (20.8 mmoles) of **29** to give 10.98 g (95%) of product, mp 162-164°. Recrystallization from absolute ethanol gave two crops, 7.70 g, mp 172-173.5° and 1.1 g, mp 165-166°. Both portions were equivalent by tlc [9:1 (v/v), chloroform-methanol] R_f 0.60, and were combined to give 8.8 g (77%). An analytical sample (recrystallized from ethanol-ether) had mp 166-167°; ir: 3300, 1445, 1242, 1025, 735 cm^{-1}; nmr (deuteriochloroform): 3.05-3.40 (m, 6, $CH_2CH_2NHCH_2$), 3.92 (s, 3, OCH_3), 4.95 (s, 2, $ArCH_2$), 5.00 (s, 2, $ArCH_2$), 5.38 (m, 1, C*H*OH), 6.50-7.00 (m, 6, Ar*H*), 7.00-7.45 (m, 10, Ar*H*).

Anal. Calcd. for $C_{31}H_{32}ClNO_4 \cdot HCl$: C, 67.15; H, 6.00; N, 2.53. Found: C, 67.43; H, 6.32; N, 2.60.

α-[[[2-(2-Chloro-4-hydroxy-3-methoxy)ethyl]amino]methyl]-4-hydroxybenzenemethanol Hydrochloride (**35**).

A 5.55 g (10 mmoles) sample of **32** was hydrogenolyzed using Procedure I. Concentration of the filtered reaction mixture gave a foam, 4.9 g (85%). Ethanol in a trace amount was occluded as judged by nmr, tlc [85:15 (v/v) chloroform-methanol]: R_f 0.15-0.20, minor 0.25-0.30, trace 0.05; ir (film): 1615, 1600, 1490, 1260, 1230, 845 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 1.16 (t, trace, CH_3CH_2OH), 2.95-3.40 (br s, 6, $CH_2CH_2NHCH_2$), 3.7 (q, trace, CH_3CH_2OH), 3.80 (s, 3, OCH_3), 5.05 (br s, 1, C*H*OH), 6.70-7.50 (m, 6, Ar*H*).

6-Chloro-2,3,4,5-tetrahydro-8-hydroxy-1-(4-hydroxyphenyl)-7-methoxy-1*H*-3-benzazepine Hydrochloride (**3**) (Procedure J').

Crude **35** (4.0 g, 9.4 mmoles) was stirred with trifluoroacetic acid (40 ml) and trifluoromethanesulfonic acid (1.21 ml, 14 mmoles) and the mixture was refluxed for 15 minutes, and the majority of the trifluoroacetic acid was removed under a stream of nitrogen. Ice was added to the residual oil, followed by 15*N* ammonium hydroxide to make the mixture basic (*p*H 8). The solid was washed with water and dried to give 3.36 g. The hydrochloride salt was obtained by dissolving the base in a small amount of methanol, then adding ethereal hydrogen chloride to give tan crystals of **3**, 2.66 g. An additional 570 mg of crude crystalline **3** (from a 2.68 mmole scale cyclization) was added to the above product to give, after three recrystallizations from methanol-acetonitrile, 1.60 g (37%): mp 290-294°; ir: 3350, 2925, 2790, 1595, 1418, 1315, 890 cm^{-1}; uv (ethanol): λ max (log ε) 282 nm (3.59), 227 s (4.26), 209 (4.68); (methanol): 282 (3.55), 224 s (4.25), 207 (4.65); ^1H ft nmr (DMSO-d_6): 2.60-3.90 (m, 6, $CH_2CH_2NHCH_2$), 3.70 (s, 3, OCH_3), 4.55 (m, 1, ArC*H*Ar), 6.12 (s, 1, Ar*H*), 6.75 (d, 2, J_{AB} = 3 Hz, Ar*H*), 6.95 (d, 2, J_{AB} = 3 Hz, Ar*H*); ^{13}C ft nmr: 26.29 (C_5), 44.14 (C_4), 44.25 (C_2), 49.44 (C_4), 59.64 (OCH_3), 115.77 ($C_{3'}$, $C_{5'}$), 115.89 (C_9), 126.79, 127.38, 130.64, 140.04 (unassigned C_{5a}, C_6, C_{9a}, $C_{1'}$); 129.26 ($C_{2'}$, $C_{6'}$), 142.03 (C_8), 149.11 (C_7), 156.51 ($C_{4'}$); ms: m/z 319 (M^+), 284, 212 (100), 181, 107.

Anal. Calcd. for $C_{17}H_{16}ClNO_3 \cdot HCl$: C, 57.32; H, 5.38; N, 3.93; Cl, 19.90. Found: C, 57.04; H, 5.61; N, 3.81; Cl, 19.54.

2-Chloro-3,4-dihydroxybenzaldehyde (**12**).

A 50 g (0.27 mole) quantity of **11** was treated with boron tribromide in dichloromethane by the method of Kaiser [12] to give a crystalline solid. Recrystallization from *n*-butyl chloride gave two crops; first crop, 34.0 g, mp 196-198°; second crop, 10.0 g, mp 193-195°, 44.0 g (95%) (lit [12] mp 193-195°). Both crops were identical by tlc (chloroform), R_f 0.15.

4-Chloro-1,3-benzodioxole-5-carboxaldehyde (**23**) [7] (Procedure F).

To 900 ml of freshly distilled dimethylformamide was added 50.0 g, (0.29 mole) of **12** and 85.5 g (1.47 mole) of potassium fluoride and the mixture was stirred for 2.5 hours at ambient temperature. The solution became dark green, but there was no exotherm. To this was added 55.6 g (0.32 mole) of dibromomethane and the mixture was heated at 115° for 1.5 hours. The mixture was cooled to ambient temperature, diluted with water and extracted with ether (3 x 300 ml). The ether extracts were washed several times with water, then with 5% sodium hydroxide (2 x 250 ml), brine, then dried (magnesium sulfate) and concentrated under vacuum to give **23** as light-tan crystals, 18.04 g, mp 121-123°. The aqueous dimethylformamide solution was further diluted with 3 ℓ water, and extracted three times with dichloromethane (1500 ml). The dichloromethane solution was washed with 5% sodium hydroxide (2 x 500 ml) and then with water until the aqueous solution was clear. The dichloromethane solution was dried (magnesium sulfate), and concentrated under vacuum to give 7.1 g of **23**, mp 120-122°. Both portions were identical by tlc (chloroform) R_f 0.65, and were combined to give 25.14 g (47%). An analytical sample was obtained by sublimation, mp 122-123°; ir: 1688, 1601, 1470, 1240, 950 cm^{-1}; nmr (deuteriochloroform): 6.19 (s, 2, OCH_2O), 6.80 (d, 1, J_{AB} = 9 Hz, Ar*H*), 7.50 (d, 1, J_{AB} = 9 Hz, Ar*H*), 12.1 (s, 1, C*H*O).

Anal. Calcd. for $C_8H_5ClO_3$: C, 52.06; H, 2.73. Found: C, 51.89; H, 2.61.

4-Chloro-1,3-benzodioxole-5-methanol (**24**).

A 25.3 g (137 mmoles) quantity of **22** was converted to **24** by Procedure B. Recrystallization of the product from *n*-butyl chloride gave 21.72 g (86%), mp 104-106°; ir: 1630, 1470, 1050, 960, 820 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 3.65 (m, 1, CH_2OH), 4.68 (d, 2, J = 3 Hz, CH_2OH), 6.05 (s, 2, OCH_2O), 6.70 (d, 1, J_{AB} = 9 Hz, Ar*H*), 7.00 (d, 1, J_{AB} = 9 Hz, Ar*H*).

Anal. Calcd. for $C_8H_7ClO_3$: C, 51.50; H, 3.78. Found: C, 51.56; H, 3.75.

4-Chloro-5-chloromethyl)-1,3-benzodioxole (**25**).

A 21.0 g (112 mmoles) quantity of **24** was converted to **25** by Procedure C. The crude product was taken up in boiling hexane and the solution was concentrated to 100 ml. The crystalline solid which formed was filtered and dried to give 19.3 g of **25** (89%), mp 94-95°. A portion was sublimed to give an analytical sample, mp 94-96°; ir: 1610, 1465, 1255, 1045, 940 cm^{-1}; nmr (deuteriochloroform): 4.65 (s, 2, CH_2Cl), 6.05 (s, 2, OCH_2O), 6.60-7.35 (m, 2, Ar*H*).

Anal. Calcd. for $C_8H_6Cl_2O_2$: C, 46.86; H, 2.95. Found: C, 47.14; H, 2.97.

4-Chloro-1,3-benzodioxole-5-acetonitrile (**26**).

An 18.64 g (91.0 mmoles) sample of **25** was converted to **26** by Procedure D. The reaction mixture was diluted with water (500 ml), and the cream-colored crystals which formed were filtered and dried to give 17.42 g (98%) of **26**, mp 126.5-128°. An analytical sample was obtained by recrystallization from *n*-butyl chloride, mp 130-131.5°. Both crystalline portions were identical by tlc (*n*-butyl chloride), R_f 0.35; ir: 2348,

1475, 1060, 950, 815 cm^{-1}; nmr (deuteriochloroform): 3.75 (s, 2, CH_2CN), 6.08 (s, 2, OCH_2O), 6.70 (d, 1, J_{AB} = 8 Hz, ArH), 6.95 (d, 1, J_{AB} = 8 Hz, ArH).

Anal. Calcd. for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; N, 7.16; Cl, 34.58. Found: C, 55.01; H, 3.03; N, 7.13; Cl, 34.43.

4-Chloro-1,3-benzodioxole-5-acetic acid (**27**).

A 16.42 g (84 mmoles) quantity of **26** was hydrolyzed by a modification of Procedure E which required that the reaction period be extended to two days to give 15.5 g (85%) of **27** mp 167-169°, with softening at 165°. An analytical sample was obtained by sublimation, mp 171.5-172.5°; ir: 1595, 1475, 1260, 950 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 3.68 (s, 2, CH_2CO_2H), 6.05 (s, 2, OCH_2O), 6.78 (br s, 2, ArH).

Anal. Calcd. for $C_9H_7ClO_4$: C, 50.37; H, 3.29. Found: C, 50.69; H, 3.22.

4-Chloro-*N*-[2-hydroxy-2-(4-methoxyphenyl)ethyl]-1,3-benzodioxole-5-acetamide (**30**).

A 15.6 g (72.5 mmoles) quantity of **27** was converted to the acid chloride and this reacted with 18.2 g (80 mmoles) of **38** by Procedure G to give 19.6 g (77%) of **30** after recrystallization from dichloromethane/*n*-butyl chloride, mp 136-137°. An analytically pure sample (from dichloromethane/*n*-butyl chloride) had mp 130.5-132.5°, mp variable, and as high as 136-137° was observed from different preparations; ir: 3250, 1635, 1470, 1250, 940 cm^{-1}; nmr (deuteriochloroform-tetradeuteriomethanol): 3.1-3.90 (m, 2, $NHCH_2CHOH$), 3.59 (s, 2, $CH_2C{=}O$), 3.82 (s, 3, OCH_3), 4.65 (m, 1, CHOH), 6.00 (s, 2, OCH_2O), 6.70 (s, 2, ArH), 6.79 (d, 2, J_{AB} = 8 Hz, ArH), 7.18 (d, 2, J_{AB} = 8 Hz, ArH).

Anal. Calcd. for $C_{18}H_{18}ClNO_5$: C, 59.42; H, 4.98; N, 3.85. Found: C, 59.61; H, 5.16; N, 3.90.

α-[[[2-4(4-Chloro-1,3-benzodioxol-5-yl)ethyl]amino]methyl]-4-methoxybenzenemethanol Hydrochloride (**33**).

A 19.6 g (44 mmoles) quantity of **30** was converted by Procedure H to give 13.56 g (65%) of **33** from ethanol, mp 172-175° with softening at 169°. An analytically pure sample was prepared from ethanol-ether: mp 169-171° with softening at 167.5°. (*NOTE*: **33** is prone to hydrogen chloride loss on drying under reduced pressure and mps as high as 172-175° were observed from different preparations); ir: 1610, 1510, 1475, 1260, 955 cm^{-1}; nmr (deuteriochloroform-tetradeuteriomethanol): 3.00-3.15 (br s, 6, $CH_2CH_2NHCH_2$), 3.80 (s, 3, OCH_3), 4.95 (m, 1, CHOH), 6.00 (s, 2, OCH_2O), 6.75 (d, 2, J_{AB} = 3 Hz, ArH), 6.80 (d, 2, J_{AB} = 8 Hz, ArH), 7.30 (d, 2, J_{AB} = 8 Hz, ArH).

Anal. Calcd. for $C_{18}H_{20}ClNO_4 \cdot HCl$: C, 55.97; H, 5.48; N, 3.63. Found: C, 56.28; H, 5.53; N, 3.51.

4-Chloro-6,7,8,9-tetrahydro-9-(4-methoxyphenyl)-5*H*-1,3-dioxolo[4,5-*h*][3]-benzazepine Hydrochloride (**36**) (Procedure J).

In trifluoroacetic acid (125 ml) was added **33** (12.54 g, 32.5 mmoles) and concentrated sulfuric acid (4.85 g, 49.5 mmoles). The solution was refluxed for 15 minutes. The trifluoroacetic acid was removed under vacuum to give an oil which was stirred with ice water and made basic with 15*N* ammonium hydroxide. The solid which formed was filtered and dissolved in chloroform. The chloroform solution was dried (potassium carbonate), filtered, saturated with hydrogen chloride gas, and concentrated under vacuum to give a solid, 12.0 g. After chromatography [400 g Silica Gel G (E. Merck), 30-70 mesh, chloroform with 0-4% methanol gradient], crystals were obtained from absolute ethanol-ether, 4.84 g (41%) of **36**, mp 244-246°; ir: 1615, 1475, 1255 cm^{-1}; nmr (deuteriochloroform): 2.50-4.00 (m, 6, $CH_2CH_2NHCH_2$), 3.78 (s, 3, OCH_3), 4.80 (br d, 1, J_{AB} = 8 Hz, ArCH), 5.95 (br s, 2, $-OCH_2O-$), 6.00 (s, 1, ArH), 6.90 (d, 2, J_{AB} = 8 Hz, ArH), 7.10 (d, 2, J_{AB} = 8 Hz, ArH).

Anal. Calcd. for $C_{18}H_{18}ClNO_3 \cdot HCl$: C, 58.71; H, 5.20; N, 3.80. Found: C, 58.35; H, 5.49; N, 4.14.

6-Chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-1-(4-methoxyphenyl)-1*H*-3-benzazepine Hydrochloride (**4**) (Procedure K).

In dry dichloromethane (90 ml) was added **36** (3.08 g, 8.36 mmoles). Boron trichloride (33.5 ml, 33.5 mmoles) was added *via* a syringe. The solution was stirred for 5 hours, and an excess of methanol was added dropwise. The solvents were removed under vacuum to give a foam. Crystals formed from ethanol to give 2.4 g (81%) of **4**, mp 267-271° dec; ir: 1605, 1510, 1300, 1245 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 3.10-3.75 (m, 6, $CH_2CH_2NHCH_2$), 3.80 (s, 3, OCH_3), 4.75-4.90 (m, 1, ArCH), 6.10 (s, 1, ArH), 6.80-7.10 (m, 4, ArH); ^{13}C ft nmr: 26.16 (C_5), 44.03 (C_4), 44.21 (C_2), 49.45 (C_1), 55.11 (OCH_3), 114.27 ($C_{3',5'}$), 114.52 (C_9), 120.94 (C_1), 126.50 (C_6), 129.34 ($C_{2',6'}$), 132.75 (C_{9a}), 134.11 (C_{5a}), 140.36 (C_7), 144.11 (C_8) 158.18 (C_4); ms: m/z 319 (M^+), 284 (100), 277, 198, 121.

Anal. Calcd. for $C_{17}H_{18}ClNO_3 \cdot HCl$: C, 57.32; H, 5.38; N, 3.93. Found: C, 57.47; H, 5.62; N, 3.75.

α-Hydroxy-4-(phenylmethoxy)benzeneacetonitrile (**37**) (Procedure L).

Using the procedure of Wagner [13], potassium cyanide (6.5 g, 0.1 mole) and ammonium chloride (5.35 g, 0.1 mole) were stirred in water (30 ml). To this stirred solution was added a slurry of 4-benzyloxybenzaldehyde (10.6 g, 50 mmoles) in ether (100 ml). The mixture was stirred vigorously for 24 hours at ambient temperature. The ether layer was separated. Crystalline material, present in the aqueous layer, redissolved upon further extraction with ether. The combined ether extracts were washed with brine and dried (sodium sulfate). The solution was filtered and concentrated to a small volume. Dilution with hexane gave a crystalline solid, mp 83-85°. Recrystallization from *n*-butyl chloride gave buff crystals, 8.32 g (70%), mp 85-87°; ir: 3300, 1510, 1250, 1020, 1010 cm^{-1}; nmr (deuteriochloroform): 2.90 (br s, 1, OH), 5.08 (s, 2, $ArCH_2$), 5.41 (s, 1, HCCN), 7.02 (d, 2, J_{AB} = 9 Hz, ArH), 7.42 (d, 2, J_{AB} = 9 Hz, ArH), 7.38 (s, 5, ArH).

Anal. Calcd. for $C_{15}H_{13}NO_2$: C, 75.30; H, 5.48; N, 5.85. Found: C, 75.18; H, 5.36; N, 6.20.

α-(Aminomethyl)-4-(phenylmethoxy)benzenemethanol Hydrochloride (**39**) (Procedure M).

Into dry tetrahydrofuran (20 ml) was added **37** (5.00 g, 20.9 mmoles). The solution was stirred and a 1.04 *M* solution of borane in tetrahydrofuran (22.7 ml, 23.6 mmoles) was added dropwise. The solution was refluxed for 3.5 hours, then distilled to near dryness. Methanol (100 ml) was added dropwise and the solution was refluxed for 45 minutes. The methanol solution was saturated with hydrogen chloride and refluxed for 15 hours, filtered and was concentrated under vacuum to an oil. Crystals formed from ethanol-ether, 5.52 g. Recrystallization from ethanol-ether gave 3.32 g (57%), mp 187-188°. An analytical sample was obtained from ethanol-ether, mp 189-190°; ir: 2900, 2850, 1605, 1505, 1245, 1090 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 2.96 (br d, 2, J = 8 Hz, CH_2NH_2), 3.20 (s, exchangeable), 4.55 (m, 1, CHOH), 5.02 (s, 2, $ArCH_2$), 6.90 (d, 2, J_{AB} = 9 Hz, ArH), 7.23 (d, 2, J_{AB} = 9 Hz, ArH), 7.36 (br s, 5, ArH), 8.32 (br m, exchangeable).

Anal. Calcd. for $C_{15}H_{17}NO_3 \cdot 1/8\ H_2O$: C, 63.88; H, 6.52; N, 4.97. Found: C, 63.78; H, 6.86; N, 4.69.

α-(Aminomethyl)-4-methoxybenzenemethanol acetate (**40**).

Following the procedure of Tinapp [14], 4-methoxybenzaldehyde (10.0 g, 73.5 mmoles) was treated with 9.03 g (86.8 mmoles) of sodium bisulfite and 5.11 g (78.7 mmoles) of potassium cyanide to give 10.51 g of a mixture of recovered aldehyde and desired cyanohydrin **38** (nmr analysis indicated **38** was 79% of the mixture). The yield, when corrected for recovered aldehyde, was 89%. To a stirred solution of this material in tetrahydrofuran (50 ml) was added a 1.07 *M* solution of borane in tetrahydrofuran (70.1 ml, 75 mmoles), and the solution was refluxed for 3 hours. The solution was concentrated, and the residual oil was cautiously diluted with methanol (125 ml) and the solution refluxed for 20 hours. The methanol was removed under vacuum, and the residual oil was dissolved in dichloromethane (175 ml) and the solution filtered. The addition of glacial acetic acid gave 8.76 g of **40** as a crystalline solid (69% based on cyanohydrin conversion), mp 123.5-124.5°; ir: 2900, 1650, 1605, 1510, 1410, 1245, 1030, 840 cm^{-1}; nmr (deuteriochloroform-DMSO-d_6): 1.85 (s, 3, CH_3CO_2-), 2.81 (m, 2, CH_2NH_3+), 3.88 (s, 3, OCH_3), 4.70 (m, 1, CHOH), 6.90 (d, 2, J_{AB} = 9 Hz, ArH), 7.40 (d, 2, J_{AB} = 9 Hz, ArH), 7.10 (s, exchangeable).

Anal. Calcd. for $C_9H_13NO_2 \cdot CH_3CO_2H$: C, 58.14; H, 7.54; N, 6.16. Found: C, 58.04; H, 7.77; N, 6.16.

Hydrolytic Preparation of 6-Chloro-2,3,4,5-tetrahydro-7-hydroxy-8-methoxy-1-(4-methoxyphenyl)-1*H*-3-benzazepine Hydrochloride (**42**) (Procedure N).

A solution of **41** (4.1 g, 13.1 mmoles in 35 ml of 12*N* hydrochloric acid was stirred at 85 ±5° for 4 hours. The solution was cooled and extracted with chloroform. The concentrated chloroform extract was chromatographed [silica gel 60, 200-400 mesh] through two columns (25 x 250 mm and 25 x 1000 mm) under medium pressure (*ca* 30 psi) at a flow rate of 7.0 ml min^{-1}, eluting with chloroform-methanol 75:25 (v/v). Fractions of 20.0 ml were collected. The product was concentrated to a foam, which was dissolved in dichloromethane. This solution was extracted with 10% sodium hydroxide. The basic aqueous solution was filtered, acidified with 12*N* hydrochloric acid, and extracted with chloroform. The chloroform solution was dried (magnesium sulfate) and concentrated to a volume of *ca* 25 ml. Ether was added to give **42** as an off-white crystalline solid, 600 mg (12%), mp 259-262°; ir: 3400, 2990, 2750, 1610, 1500, 1255, 1000 cm^{-1}; ^1H ft nmr (deuteriochloroform-tetradeuteriomethanol): 2.80 (s, 2, exchangeable), 2.95-4.00 (m, 6, $CH_2CH_2NHCH_3$), 3.60 (s, 3, OCH_3), 3.80 (s, 3, OCH_3), 4.70 (br d, 1, J_{AB} = 4 Hz, ArC*H*Ar), 6.18 (s, 1, Ar*H*), 6.80 (d, 2, J_{AB} = 8 Hz, Ar*H*), 7.05 (d, 2, J_{AB} = 8 Hz, Ar*H*); ms: m/z 333 (M^+), 298 (100), 291, 212, 121.

Anal. Calcd. for $C_{18}H_{28}ClNO_3 \cdot HCl \cdot 1/2\ H_2O$: C, 57.00; H, 5.85; N, 3.69. Found: C, 57.14; H, 5.77; N, 3.79.

A later preparation of **42** utilized highly purified **41**, treated identically. The initial chloroform extract was concentrated to a foam which gave crude crystalline **42** from acetonitrile containing a little methanol in 78% yield.

Hydrolytic Preparation of 6-Chloro-2,3,4,5-tetrahydro-7-hydroxy-1-(4-hydroxyphenyl)-8-methoxy-1*H*-3-benzazepine Hydrochloride (**2**) (Procedure N[1]).

Under nitrogen, **41** (10.0 g, 260 mmoles) was stirred in 200 ml of 12*N* hydrochloric acid, and heated at 100 ±1° for 13 hours. The mixture turned purple, and a gum formed. The mixture was stirred with chloroform, and the liquid phases were decanted. The gum (which was soluble in neither aqueous acid nor chloroform) was triturated with boiling methanol. The methanol-insoluble material was filtered, giving pink-tinged crystals, 1.0 g. The filtrate was concentrated under vacuum to a purple foam, 6.28 g. This material was dissolved in 35 ml methanol and diluted with 40 ml acetonitrile to give crystals, 1.0 g. An additional crop of crystalline solid, 1.60 g, formed from the combined acid/chloroform extracts. All crops of crystalline solid were combined and triturated with boiling chloroform for 3 hours and then filtered to give 2.3 g of **2**. Recrystallization from methanol gave white plates, 1.96 g (21%), mp 297° dec; ir, uv, ^1H-ft nmr, ^{13}C-ft nmr and ms spectra were all essentially superimposable with those obtained from the acid-cyclized preparation of this compound (see above).

A later preparation of **2** utilized highly purified **41**, treated identically. A white crystalline solid formed in the reaction mixture which was recrystallized from methanol/ether to give a 33% yield of **2**, mp 295-296° dec.

Pharmacology - Selective Renal Vasodilator Activity [2].

Vasodilator activity was measured in anesthetized dogs surgically prepared for electromagnetic measurement of renal artery blood flow. Blood pressure was measured from the carotid artery, and drugs were infused into an antecubital vein. Heart rate was recorded by a cardiotachometer triggered by the electrocardiogram. Vascular resistance was calculated as the ratio of mean arterial blood pressure to mean blood flow. Cumulative dose-response data were obtained by infusing the drug at progressively increasing (usually threefold) concentrations, each dose level being infused for 5 minutes. For comparison, the potency of each compound is expressed as the average minimum cumulative dose which decreases renal vascular resistance (RVR) by 15%. The maximum renal vasodilator effect is expressed as the average maximum percent decrease in RVR attainable with the compound.

Adenylate Cyclase.

The cAMP formed in caudate homogenates was measured by a modification of the procedures described by Kebabian *et al.* [15] and Carenzi *et al.* [16]. Charles River male rats weighing 225-300 g were killed by cervical dislocation followed by decapitation and the caudate nuclei rapidly dissected on ice. The caudates were gently homogenized at 0° by hand using a Teflon-glass homogenizer in 50 volumes of 50 mM Tris-maleate buffer (*p*H 7.4) containing 2 mM EGTA. Aliquots (50 µl) of the homogenate were transferred to 250 µl of incubation medium containing 80 mM Tris-maleate buffer (*p*H 7.4), 2 mM magnesium sulfate, 0.2 mM EGTA, 5 mM aminophylline, 0.05% sodium-metabisulfite and test substances as required. Lastly 20 µl of 10mM ^{14}C-ATP (final concentration 0.65 mM), approximately 1.5 x 10^{-6} dpm/sample, was added quickly to all tubes on ice. The reaction was initiated by shaking at 30° and incubation continued for 3 minutes. The reaction was terminated in a boiling water bath for 3 minutes. Distilled water (600 µl) was added and mixed with each sample.

The ^{14}C-cAMP formed was separated from the ^{14}C-ATP using alumina and cation exchange resin columns as described by Guidotti *et al.* [17] using the entire sample. The 4 ml cAMP fraction from the Dowex 50 column was collected in scintillation vials, 10 ml of Aquasol-2 (New England Nuclear) added, the vials shaken vigorously to form a gel and the ^{14}C content determined by liquid scintillation spectrometry. The cAMP content was calculated using the specific activity of the ^{14}C-ATP. The standard deviation of quadruplicate samples was less than 10% of the mean value. Results are reported as the EC_{50} which is the concentration of the compound that produces 50% of its maximal increase of c-AMP. The IC_{50} is the concentration of compound required to inhibit by 50% the stimulation of c-AMP formation produced by 50 µM dopamine.

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