Dopaminergic Activity of Substituted 6-Chloro-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines

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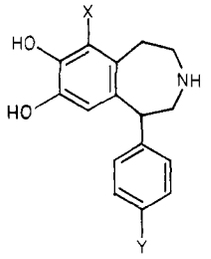
6-Chloro-7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepines were synthesized and evaluated as agonists of central and peripheral dopamine receptors. These benzazepines were prepared by cyclization of certain amino alcohols followed by demethylation of the 7,8-dimethoxy groups of the precursors to the 7,8-catecholic moiety. Preliminary evidence of dopaminergic activity was determined in anesthetized dogs by measuring the effects on renal blood flow and calculating the accompanying changes in renal vascular resistance. The most potent compounds contained an hydroxyl group on the 1-phenyl group or were substituted at the 3′ position with a chloro, methyl, or trifluoromethyl group. Evidence for central dopaminergic activity was obtained by measuring rotational effects in rats lesioned in the substantia nigra and also in an in vitro assay which measured stimulation of rat striatal adenylate cyclase. The compounds with the best central dopaminergic activity were generally the benzazepines which were the most lipophilic, were substituted on the 3′ position of the 1-phenyl group, and contained either a 3-*N*-methyl or 3-*N*-allyl group.

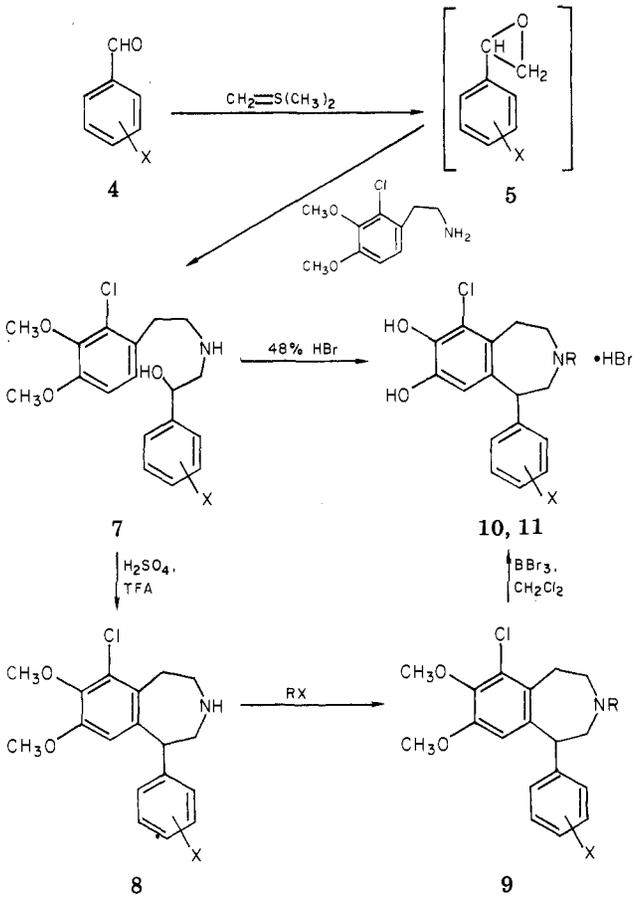
Dopaminergic receptors have been identified in the central nervous system and in the periphery.[2-7] Recent reports from our laboratories[4] have described the profiles of dopamine agonists[8-11] and antagonists.[12] The central and peripheral dopaminergic activities of **1**, 7,8-dihydroxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SK&F 38393), were reported,[8,9] and the selective peripheral dopamine agonist activity of **2**, 6-chloro-7,8-dihydroxy-1-(4-hydroxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (SK&F 82526), was demonstrated.[11] In contrast to the substantial renal vasodilator activity exhibited by **2**, the 6-dechloro derivative **3** was inactive as a renal vasodilator.[11] This paper describes the SAR of other 6-chloro derivatives of **2** with chemical modifications on the 3-benzazepine nucleus aimed at functionalization of the 3-nitrogen and substitution on the 1-phenyl ring. On the basis of the earlier studies reported with compounds in this series, we have interpreted increases in renal blood flow (dog) as evidence for the activation of renal dopamine receptors. Similarly, we have interpreted contralateral rotational effects in rats with a unilateral lesion in the substantia nigra and activation of dopamine-sensitive rat striatal adenylate cyclase (in vitro) as evidence for centrally mediated dopaminergic activity.



1 (SK&F 38393), X = Y = H
2 (SK&F 82526), X = Cl; Y = OH
3, X = H; Y = OH

Chemistry. The synthesis of the 3-benzazepines is shown in Scheme I. The requisite aldehydes **4** were converted to the oxiranes **5** via dimethylsulfonium methylide,[13] and the crude oxiranes **5** were heated at 110 °C with 2-chlorohomoveratrylamine (**6**)[11] to produce the amino alcohols **7** (see Table IV). Compounds **7** were usually purified by direct crystallization of the reaction mixture or, when necessary, by column chromatography, since it was beneficial to use clean **7** for cyclization to the 3-

Scheme I



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(2) L. I. Goldberg, *Pharmacol. Rev.*, **24**, 1 (1972).
(3) (a) L. L. Iverson, *Science*, **188**, 1084 (1975); (b) J. G. Cannon, *Adv. Biosci.*, **20**, 87 (1978).
(4) P. E. Setler, R. G. Pendleton, and E. Findlay, *J. Pharmacol. Exp. Ther.*, **192**, 702 (1975).
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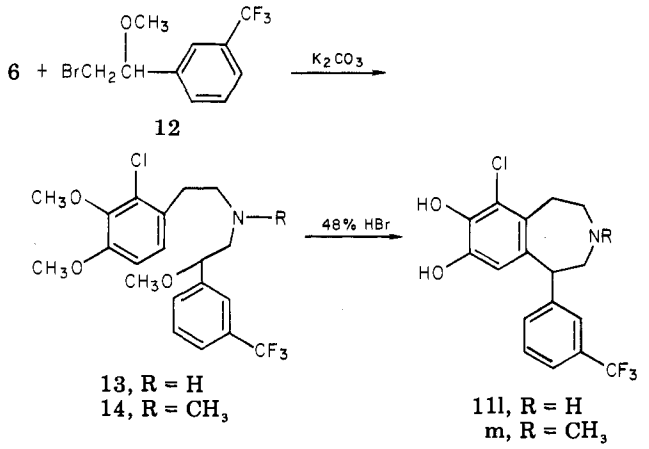
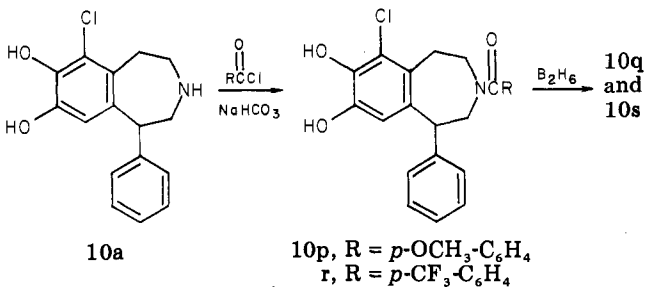
Scheme II



Scheme III



benzazepines. When compounds 7 were heated at 115 °C with 48% HBr, the 7,8-dihydroxy-3-benzazepines 10 and 11, which are listed in Table I, were isolated directly as the HBr salts. Cyclization of 7 with H_2SO_4 in CF_3COOH at 25 °C gave the 7,8-dimethoxy-3-benzazepines 8 shown in Table II, which were then alkylated or acylated on nitrogen prior to cleavage of the methyl ethers with BBr_3 in CH_2Cl_2. The *m*-trifluoromethyl derivatives **11l** and **11m** were prepared by an alternative procedure as shown in Scheme II. 2-[3-(Trifluoromethyl)phenyl]-2-methoxyethyl bromide (**12**)[14] was heated with **6** and K_2CO_3 to give **13**, which was converted to **14**. Subsequent treatment of **13** and **14** with hot HBr gave 6-chloro-7,8-dihydro-1-[3-(trifluoromethyl)phenyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrobromides **11l** and **11m**. Scheme III portrays the preparation of the amides **10p** and **10r** from **10a** and the reduction of these amides with diborane to the benzyl derivatives **10q** and **10s** (see Table I).

Structure–Activity Relationships. The biological activities of the benzazepines are summarized in Tables I and III. Effects on systemic blood pressure (MABP), heart rate (HR), and renal blood flow (RBF) were measured in anesthetized dogs by techniques previously described.[9-11] Renal vasodilator activity was first determined qualitatively. The renal vascular resistance (RVR) was calculated as the ratio of the MABP to mean RBF. Other details of this protocol can be found in Table I. The most active compounds from the primary renal vasodilator screen were then subjected to a secondary analysis, and these results are listed in Table III. Cumulative dose–response data were obtained by infusing the drug at progressively increasing infusion rates, and each dose level was infused for 5 min. The potency for each compound is expressed as the average minimum cumulative dose which decreased RVR by 15%. The maximum renal vasodilator effect is expressed as the average maximum percent decrease in RVR attainable with the compound. The selectivity ratios are the separations between the RVR ED_{15} and doses producing a 30% change in iliac vascular resistance (IVR), a 20% change in MABP, and a 20% change in HR. Drug effects on central dopaminergic activity were determined by procedures and parameters described previously,[8] and the test results are listed in Table I.

It can be seen in Table I that **10a**, the prototype for this series of compounds, has both central and peripheral activity. Compound **10a** is equipotent to dopamine as a renal vasodilator and is more active than dopamine in its central effects.[11] The 7,8-diacetoxy derivative **10b** was equipotent to **10a** as a renal vasodilator, suggesting that 7,8-diesters are prodrug equivalents of the catecholic moiety. The 3-*N*-methylbenzazepines **10c,d,w** and **11h,m** were essentially inactive in the primary renal vasodilator screen, indicating that secondary amines are usually required for optimal activity. The exceptions are the allyl derivatives **10j**, **10x**, **11j**, and the 2-furanylmethyl derivative **10m**. Other *N*-alkyl derivatives **10e–h** were marginally active in reducing renal vascular resistance. The 3-*N*-2-thienylmethyl analogue **10n**, in contrast to **10m**, was significantly but marginally active at the highest test dose. Functionalization on nitrogen with the relatively large benzyl group para substituted with a methoxyl (**10q**) or a trifluoromethyl (**10s**) was not particularly beneficial.

All of the above benzazepines contained an unsubstituted 1-phenyl group. Variations on the 1-phenyl group have provided compounds with exceptional activity. The 4′-hydroxy analogue (**2**) of **10a** exhibited outstanding activity as a renal vasodilator;[11] the 3′-hydroxy isomer **10t** showed good activity but of lowered magnitude relative to **2**. The 4′-chloro derivative **10u** did not significantly increase RBF; however, the 3′-chloro isomer **10v** was very significantly active and its 3-*N*-allyl derivative **10x** showed good activity. The combination of hydroxyl and halo groups on the 1-phenyl afforded **10z** and **11a–d**, with the 4′-chloro-3′-hydroxyl derivatives **11a,b** being the most potent. The 3′,5′-dichloro-4′-hydroxyl **11c** was less active than **11a**. Substitution of a methyl group at the 2′ and 4′ positions (**11e,f**) did not enhance activity, but the 3′-methyl **11g** and the corresponding *N*-3-allyl **11j** exhibited good activity as renal vasodilators. Other 3′-functionalized analogues, including the trifluoromethyl derivative **11l**, were modestly active.

The most active renal vasodilators listed in Table I were then studied more rigorously, and the results of these investigations are shown in Table III. Compound **2** was clearly the most potent benzazepine, and it also showed

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(12) C. Kaiser, F. E. Ali, W. E. Bondinell, M. Brenner, K. G. Holden, T. W. Ku, H. Oh, S. T. Ross, N. C. F. Yim, C. L. Zirkle, R. A. Hahn, H. M. Sarau, P. E. Setler, and J. R. Wardell, Jr., *J. Med. Chem.*, **23**, 976 (1980).
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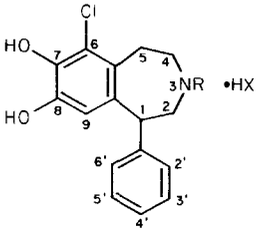
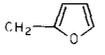
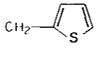
Table I. 6-Chloro-7,8-dihydroxy-3-benzazepines (10 and 11)

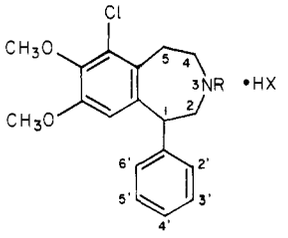


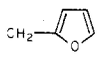
compd	4′	3′	2′	R	X	mp, °C	recrystn solvent[c]	renal vasodilator act.[a] RBF	renal vasodilator act.[a] RVR	central dopaminergic act.[b] RD_{500}, mg/kg ip	contralateral rotation in lesioned rats RD_{1000}, mg/kg po	contralateral rotation in lesioned rats RD_{500}, μg/rat ic	rat striatal adenylate cyclase: % DA response or EC_{50}, M	formula	anal.[g]
10a	H	H	H	H	Br	*d*		++[e]	++	0.03 (0.21-0.75)[f]	4.04 (2.87-6.44)	0.22 (0.07-1.55)	1×10^{-8}		
10b	H	H [7,8-$(OAc)_2$]	H	H	Cl	234-235	A	++	++					$C_{20}H_{20}ClNO_4 \cdot HCl$	C, H, N
10c	H	H	H	CH_3	Cl	183-185	B	+	+	0.03 (0.02-0.05)		0.32 (0.18-0.62)	6×10^{-7}	$C_{17}H_{18}ClNO_2 \cdot HCl$[h]	C, H, N, Cl
10d	H	H [7,8-$(OAc)_2$]	H	CH_3	Cl	153-155	A	I[i]		0.025	2.2			$C_{20}H_{24}ClNO_2 \cdot HCl$[h]	C, H, N
10e	H	H	H	CH_2CH_3	Br	208-210	D	++	++	0.015 (0-0.04)	4.9		55 @ 10^{-5} 48 @ 10^{-6}	$C_{18}H_{20}ClNO_2 \cdot HBr$	C, H, N
10f	H	H	H	CH_2CH_2OH	Br	135-137	A	+	I	10 mg/kg, 1306 ± 252 turns/2 h				$C_{18}H_{20}ClNO_3$	C, H, N
10g	H	H	H	$(CH_2)_2CH_3$	Br	208-210	C	+	I	2 mg/kg I[i]				$C_{19}H_{22}ClNO_2 \cdot HBr$	C, H, N
10h	H	H	H	$(CH_2)_3CH_3$	Br	183-185	C	I		10 mg/kg, 611 ± 167 turns/2 h			90 @ 10^{-5} 85 @ 10^{-6}	$C_{20}H_{24}ClNO_2 \cdot HBr$	C, H, N
10j	H	H	H	$CH_2CH{=}CH_2$	Br	203-204	B	++	++	0.03 (0.02-0.04)			85 @ 10^{-6} 43 @ 10^{-8}	$C_{19}H_{20}ClNO_2 \cdot HBr$	C, H, N
10l	H	H [7,8-$(OAc)_2$]	H	$CH_2CH{=}CH_2$	Cl	168-170	E			0.03	10 mg/kg I			$C_{23}H_{24}ClNO_4 \cdot HCl$	C, H, N
10m	H	H	H		Cl	239-241	D	++	++	10 mg/kg, 611 ± 167 turns/2 h			82 @ 10^{-5} 41 @ 10^{-6}	$C_{21}H_{20}ClNO_3 \cdot HCl$[h]	C, H, N
10n	H	H	H		Cl	238-240	F	+	+	0.063	5.8		64 @ 10^{-5} 51 @ 10^{-6}	$C_{21}H_{20}ClNO_2S \cdot HCl$	C, H, N
10p	H	H	H	COC_6H_4-*p*-OCH_3		224-225	F							$C_{24}H_{22}ClNO_4$	C, H, N
10q	H	H	H	$CH_2C_6H_4$-*p*-OCH_3	Cl	191-193	G	++	++	10 mg/kg I				$C_{24}H_{24}ClNO_3 \cdot HCl$[k]	C, H, N
10r	H	H	H	COC_6H_4-*p*-CF_3		244-245	G							$C_{24}H_{19}ClF_3 \cdot NO_3$	C, H, N
10s	H	H	H	$CH_2C_6H_4$-*p*-CF_3	Cl	239-241	F	+	I	10 mg/kg, 455 ± 163 turns/2 h				$C_{24}H_{21}ClF_3 \cdot NO_2 \cdot HCl$	C, H, N
2	OH	H	H	H	CH_3SO_3	*d*		++	++	10 mg/kg I		0.5 (0.4-0.8)			

10t	H	OH	H	H	Br	217-219	D	+	+	10 mg/kg I		4.5 × 10^{-8}	$C_{16}H_{16}ClNO_3$·HBr	C, H, N
10u	Cl	H	H	H	Br	253-256	C	I		3.4 (0.01-0.63)	5.8 mg/kg I	68 @ 10^{-5} 52 @ 10^{-6}	$C_{16}H_{15}Cl_2NO_2$·HBr[l]	C, H, N
10v	H	Cl	H	H	Br	245-247	C	++	I	0.3	10 mg/kg, 602 ± 268 turns/2 h	90 @ 10^{-5} 82 @ 10^{-6}	$C_{16}H_{15}Cl_2NO_2$·HBr[m]	C, H, N
10w	H	Cl	H	CH_3	Br	263-265	H	I		0.03	3.2 (2.24-6.3)	13 @ 10^{-5} 22 @ 10^{-6}	$C_{17}H_{17}Cl_2NO_2$·HBr	C, H, N
10x	H	Cl	H	$CH_2CH{=}CH_2$	Br	250-252	A	++	I	0.11	10 mg/kg, 1163 ± 522 turns/4 h	83 @ 10^{-5} 92 @ 10^{-6}	$C_{19}H_{19}Cl_2NO_2$·HBr	C, H, N
10y	H	Cl	H		Cl	241-243	H	+	I		6 mg/kg I		$C_{21}H_{19}Cl_2NO_3$·HCl[n]	C, H, N, Cl[o]
10z	OH	Cl	H	H	Br	294-296	H	+	I	10 mg/kg I			$C_{16}H_{15}Cl_2NO_3$·HBr	C, H, N
11a	Cl	OH	H	H	Br	268-270	H	++	++	10 mg/kg I			$C_{16}H_{15}Cl_2NO_3$·HBr	C, H, N
11b	Cl	OH	H	$CH_2CH{=}CH_2$	Br	183-186	H	++	+	10 mg/kg I			$C_{19}H_{19}Cl_2NO_3$·HBr[k]	C, H, N
11c	OH	Cl	5'-Cl	H	Br	290-292	H	+	+	10 mg/kg I			$C_{16}H_{14}Cl_3NO_3$·HBr[p]	C, H, N
11d	OH	Br	H	H	Br	180-185	H	*q*					$C_{16}H_{15}BrClNO_3$·HBr[k,r]	C, H, N, Br
11e	CH_3	H	H	H	Br	260-263	A	I		10 mg/kg, 420 ± 104 turns/2 h		42 @ 10^{-5} 23 @ 10^{-6}	$C_{17}H_{18}ClNO_2$·HBr	C, H, N
11f	H	H	CH_3	H	Br	234-236	J	I		10 mg/kg, 663 ± 138 turns/2 h		55 @ 10^{-5} 30 @ 10^{-6}	$C_{17}H_{18}ClNO_2$·HBr[m]	C, H, N
11g	H	CH_3	H	H	Br	243-245	J	++	++	0.47 (0.3-0.96)		94 @ 10^{-5} 76 @ 10^{-7}	$C_{17}H_{18}ClNO_2$·HBr	C, H, N
11h	H	CH_3	H	CH_3	Br	263-265	H	I		0.041	2.0	14 @ 10^{-5} 15 @ 10^{-6}	$C_{18}H_{20}ClNO_2$·HBr	C, H, N
11j	H	CH_3	H	$CH_2CH{=}CH_2$	Br	265-267	H	++	++	0.04	3.0	96 @ 10^{-5} 86 @ 10^{-7}	$C_{20}H_{22}ClNO_2$·HBr	C, H, N
11k	H	CH_3	H		Cl	262-265	H	I		2.0 mg/kg I			$C_{22}H_{22}ClNO_3$·HCl	C, H, N
11l	H	CF_3	H	H	Br	165-169	K	++	++	0.71 (0.21-1.18)	5.8 mg/kg/I	64 @ 10^{-5} 59 @ 10^{-6}	$C_{17}H_{15}ClF_3NO_2$·HBr[s]	C, H, N
11m	H	CF_3	H	CH_3	Br	264-266	L	I		2.0 mg/kg, 594 ± 172 turns/2 h	6.0 mg/kg, 296 ± 204 turns/2 h		$C_{18}H_{17}ClF_3NO_2$·HBr	C, H, N
dopamine								++	++			0.10 (0.08-1.3)	3.5 × 10^{-6}	

[a] Renal blood flow (RBF) was measured in dogs using the protocol described in ref 11. Test drug was separately infused at increments of 0.3, 3, 30, and 300 (μg/kg)/min at approximately 15-min intervals, each infusion being of 5-min duration. The renal vascular resistance (RVR) was calculated as the ratio of the mean arterial blood pressure/mean RBF. Minimum changes (%) which are considered significant: one dog, RBF ±8.4 and RVR ±13.2; two dogs, RBF ±5.9 and RVR ±9.3; three dogs RBF ±4.8 and RVR ±7.6. [b] See ref 8 for details of methodology; RD_{500} and RD_{1000} are the minimum concentrations producing 500 and 1000 turns, respectively, in 2 h. [c] Recrystallization solvents: A, MeOH-ether; B, 2-propanol-ether; C, 2-propanol; D, MeCN; E, $CHCl_3$-ether; F, MeOH-EtOAc; G, MeOH; H, MeOH-MeCN; J, MeOH-2-propanol; K, H_2O; L, EtOH. [d] See ref 11. [e] Significant activity is defined as + within the limits described in footnote *a*, and ++ is highly significant activity. [f] 95% confidence limits. [g] Analytical results in this table were within ±0.4 of the theoretical values. [h] Calculated for 0.25 mol of H_2O. [i] Inactive as defined in footnote *e*. [k] Calculated for 0.75 mol of H_2O. [l] Calculated for 0.33 mol of 2-propanol. [m] Calculated for 0.5 mol of 2-propanol. [n] Calculated for 0.9 mol of HCl and 2.25 mol of H_2O. [o] Ionic Cl: calcd, 8.04; found, 7.38. [p] Calculated for 0.75 mol of MeOH. [q] See Table III. [r] Calculated for 0.25 mol of MeCN. [s] Calculated for 0.5 mol of H_2O.

Table II. 6-Chloro-7,8-dimethoxy-3-benzazepines (8 and 9)



compd	4'	3'	R	X	mp, °C	recrystn solvent[a]	formula	anal.[b]
8a	H	H	H	Cl	243-244	A	$C_{18}H_{20}ClNO_2 \cdot HCl$	C, H, N
9a	H	H	CH_3	Cl	233-234	B	$C_{19}H_{22}ClNO_2 \cdot HCl$	C, H, N
8b	H	Cl	H	Cl	160-163	C	$C_{18}H_{19}Cl_2NO_2 \cdot HCl$[c]	C, H, N
9b	H	Cl	CH_3	fumarate	197-199	D	$C_{19}H_{21}Cl_2NO_2 \cdot C_4H_4O_4$	C, H, N
9c	H	Cl	$CH_2CH{=}CH_2$	Cl	192-194	C	$C_{21}H_{23}Cl_2NO_2 \cdot HCl$	C, H, N
8c	H	CH_3	H	Cl	132-140	E	$C_{19}H_{22}ClNO_2 \cdot HCl$	C, H, N
9d	H	CH_3	CH_3	fumarate	185-187	E	$C_{20}H_{24}ClNO_2 \cdot C_4H_4O_4$	C, H, N
9e	H	CH_3	$CH_2CH{=}CH_2$	Cl	178-180	F	$C_{22}H_{27}ClNO_2 \cdot HCl$	C, H, N
9f	H	CH_3		Cl	235-237	B	$C_{24}H_{26}ClNO_3 \cdot HCl$[d]	C, H, N
9g	Cl	OCH_3	$CH_2CH{=}CH_2$	Cl	163-165	D	$C_{22}H_{25}Cl_2NO_3 \cdot HCl$	C, H, N

[a] Recrystallization solvents: A, 2-propanol-ether; B, MeOH-ether; C, acetone-ether; D, EtOH; E, acetone; F, EtOAc. [b] Analytical results in this table were within ±0.4 of the theoretical values. [c] Calculated for 0.5 mol of H_2O. [d] Calculated for 0.25 mol of H_2O.

Table III. Renal Vasodilator Activity[a]

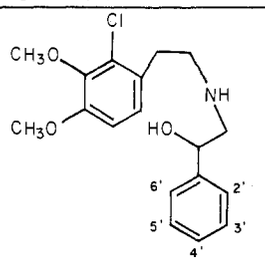
compd	RVR ED_{15},[b] μg/kg iv	av max % ↓ RVR	IVR ED_{30}/ RVR ED_{15}	MABP ED_{20}/ RVR ED_{15}	HR ED_{20}/ RVR ED_{15}
10a	3.5 (2)	39	628	>1734	108
10e	45 (2)	16	0.1	18	>6072
10f	4.5 (3)	42	929	>6072	>6072
10m	200 (2)	26	>6072	>6072	>6072
2	0.3 (5)	59	>6072	>6072	>6072
10t	0.35 (2)	49	34	>6072	1029
10x	22 (2)	38	>6072	>6072	>6072
10z	99 (3)	56	−1	−3	0
11a	61 (3)	25	>249	>249	>249
11b	19 (3)	39		>319	>319
11c	165 (4)	18	>37	>37	>37
11d	2 (2)	26	15	>2995	>2995
11g	15 (3)	56	1	>6072	7
11l	8 (2)	44	10	>6072	75
dopamine	2.7 (3)	36	56	113	141

[a] See ref 11 for details of methodology for determining RVR ED_{15}, average maximum percent decrease in RVR, and the selectivity ratios ED_{15} relative to iliac vascular resistance (IVR), mean arterial blood pressure (MABP), and heart rate (HR). The following changes were determined to be the minimum necessary for statistical significance ($p = 0.95$): RVR, 16%; MABP, ±6%; IVR, ±24%; HR, ±9%. [b] Number of dogs used in test are in parentheses.

excellent selectivity for the renal vasculature. The 3'-hydroxy analogue **10t** was nearly as potent as **2** but was not as selective. Compound **10x** exhibited excellent selectivity ratios, but was 70 times less potent than **2**. Compound **10a** was one-tenth as potent as **2** and was not selective for the renal vasculature. In summary, the renal vasodilator data show that of the 6-chlorobenzazepines, (1) the hydroxy-substituted 1-phenyl derivatives are the most active, (2) the 3' position of the 1-phenyl group substituted with hydroxyl, chloro, methyl, or trifluoromethyl provided active compounds, (3) the 3-*N*-allyl group imparts activity in those derivatives in which the corresponding 3-*N*-methyl derivatives were inactive, and (4) the 3-benzazepines not derivatized on nitrogen were the most potent compounds.

The relationships between structure and central dopaminergic activities are found in Table I. The compounds were routinely tested for contralateral rotation in lesioned rats by intraperitoneal (ip) administration. Oral activity (po) was a primary goal for a central dopaminergic agonist, and the more active compounds were studied for this potential use. Intrinsic activity was measured by intracaudal (ic) administration. Compound **10a** has potent central dopaminergic activity as can be seen in the ip, po, and ic rotation test results and by the high activity as a stimulant of rat striatal adenylate cyclase. The *N*-methyl (**10c**), *N*-ethyl (**10e**), and *N*-allyl (**10j**) derivatives of **10a** exhibited good activity in the rat rotation and cyclase tests, but the 7,8-diacetoxy (**10l**) derivative of **10j** was orally inactive at 10 mg/kg. Compound **10n** was one-half as potent as **10a** in the rat rotation test. The 4'- and 3'-hydroxy analogues (**2** and **10t**) were inactive by ip administration, but by the ic route **2** was shown to have good intrinsic activity. Compounds with the 1-phenyl group substituted with a chloro (**10u–x**) were about one-tenth as active as **10a**, and **10x** was the most active. Compound **10x** also was a good stimulator of rat striatal adenylate cyclase. The 3'-methyl analogues **11g**, **11h**, and **11j** were clearly potent in the rat rotation tests, and compound **11j** was the most active. Compound **11l** was active when administered ip but was

Table IV. Amino Alcohol Precursors of 3-Benzazepines (7)



compd	4′	3′	2′	mp, °C	recrystn solvent	yield,[a] %	formula	anal.
7a	H	OCH_3	H	96-97	acetone–ether	7	$C_{19}H_{24}ClNO_4$	C, H, N
7b	Cl	H	H	99-100	EtOH	10.5	$C_{18}H_{21}Cl_2NO_3$	C, H, N
7c	H	Cl	H	164-165	EtOH	21	$C_{18}H_{21}Cl_2NO_3$	C, H, N
7d	OCH_3	Cl	H	115-117	EtOH	9	$C_{19}H_{23}Cl_2NO_4$	C, H, N
7e	Cl	OCH_3	H	123-125	EtOH	17	$C_{19}H_{23}Cl_2NO_4$	C, H, N
7f	OCH_3	Cl	5′-Cl	116-118	EtOH	10	$C_{19}H_{22}Cl_3NO_4$	C, H, N
7g	OCH_3	Br	H	131-133	MeOH	17	$C_{19}H_{23}BrClNO_4$	C, H, N, Br
7h	CH_3	H	H	117-118	EtOH	12	$C_{19}H_{24}ClNO_3$	C, H, N
7i	H	CH_3	H	98-99	EtOH	10	$C_{19}H_{24}ClNO_3$	C, H, N
7j	H	H	CH_3	116-118	EtOH	11	$C_{19}H_{24}ClNO_3$	C, H, N
7k	CF_3	H	H	109-110	EtOH	12	$C_{19}H_{21}ClF_3NO_3$	C, H, N

[a] Yields were calculated from the substituted benzaldehydes.

inactive when given orally. All of the other compounds were less potent or inactive. In summarizing the central dopaminergic actions of these benzazepines, it can be seen that (1) the most lipophilic compounds exhibit the best activity in the rat rotation tests, (2) the 3′ position on the 1-phenyl group when substituted with chloro, methyl, or trifluoromethyl provide compounds with enhanced activity when compared to the 2′ and 4′ analogues, and (3) the *N*-methyl and *N*-allyl derivatives impart good central dopaminergic activity to these benzazepines.

Experimental Section

Column chromatography was carried out on Merck silica gel 60 (MC/B, Cincinnati, OH). Proton magnetic spectra were run on Varian T-60 and Varian EM-360 (60 MHz) instruments using Me_4Si as reference. Infrared spectra were run on a Perkin-Elmer Infracord Model 137. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. TLC's were run on Uniplate precoated silica gel plates, 250 μm (Analtech, Inc., Newark, DE). Solvents were dried over $MgSO_4$. *m*-Anisaldehyde, *m*- and *p*-chlorobenzaldehydes, and *o*-, *m*-, and *p*-tolualdehydes were commercial samples which were not purified. 3-Chloro-4-methoxybenzaldehyde and 3,5-dichloro-4-methoxybenzaldehyde were prepared as described.[15] 4-Chloro-3-methoxybenzaldehyde was synthesized from 4-chloro-3-methoxybenzoic acid[16] by reduction with B_2H_6 to the benzyl alcohol, followed by oxidation with activated MnO_2 at 80 °C in toluene. 3-Bromo-4-methoxybenzaldehyde[17] was also prepared by a redox procedure. 4-(Trifluoromethyl)benzaldehyde was obtained by hydrolysis of the oxime[18] at 25 °C with 3 N HCl in MeCN in the presence of excess CH_3CHO. All compounds were routinely checked by IR, NMR, TLC, and mass spectroscopy. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

3-Bromo-4-methoxy-α-[[*N*-(2-chloro-3,4-dimethoxyphenethyl)amino]methyl]benzyl Alcohol (7g). A suspension of 14 g (0.28 mol) of 50% NaH in mineral oil in 300 mL of Me_2SO was heated at 65–70 °C for about 80 min to give a nearly clear, greenish solution. Then 150 mL of dry THF was added, and the mixture was cooled in ice–H_2O. A solution of 57.2 g (0.28 mol) of trimethylsulfonium iodide[13] in 400 mL of Me_2SO was added over 10 min. After the mixture was stirred for an additional 5 min, a solution of 40 g (0.186 mol) of 3-bromo-4-methoxybenzaldehyde in 150 mL of THF was added over 10 min. The mixture was stirred at 0 °C for 15 min and then at 25 °C for 2 h, diluted with 4 L of ice–H_2O, and extracted several times with EtOAc, and the extracts were washed with brine. The dried crude oxirane **5** (38 g) (TLC with cyclohexane/EtOAc, 3:2, showed one major material with an R_f of 0.48) was mixed with 30 g (0.14 mol) of 2-(2-chloro-3,4-dimethoxyphenyl)ethylamine (**6**)[11] and heated at 110 °C for 18 h under N_2. The cooled reaction mixture was triturated with EtOAc to give a voluminous solid, which was collected and washed with 1:1 EtOAc–petroleum ether to afford 20.5 g (17%) of **7g**. An analytical sample was prepared from EtOH. Table IV lists other amino alcohols (**7**) which were prepared using the same conditions. When crystallization could not be induced directly, purification was achieved by column chromatography on silica gel with a 0.5 to 2% of MeOH in CH_2Cl_2 gradient.

6-Chloro-7,8-dimethoxy-1-(3-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (8b). In 50 mL of CF_3COOH was dissolved 7.5 g (0.02 mol) of **7c**, and then 2.5 mL of H_2SO_4 was added. The solution was refluxed for 2 h, concentrated in vacuo, basified with cold NaOH solution, and extracted with EtOAc. After the solution was washed with H_2O, the dried, concentrated product (7.5 g) (TLC with EtOAc/MeOH/NH_4OH, 75:23:2, showed one spot with an R_f of 0.55) was converted to the hydrochloride salt with ethereal HCl to provide white powdery **8b**·HBr. In Table II are listed other benzazepines prepared by this method.

6-Chloro-7,8-dimethoxy-3-methyl-1-(3-chlorophenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9b). A solution of 3 g (8.5 mmol) of **8b**, 15 mL of 37% HCHO, and 18 mL of 88% HCOOH was heated on the steam bath for 4.5 h, diluted with ice, and basified with NaOH solution, and the product was extracted into EtOAc and washed with H_2O. The crude material (2.6 g) was chromatographed on 125 g of silica gel with a 1 to 2% of MeOH in CH_2Cl_2 gradient to give 2.2 g (71%) of homogenous **9b** (TLC with 4% MeOH in CH_2Cl_2 showed an R_f 0.85). A fumarate salt was prepared with ethanolic fumaric acid. In Table II are listed other 3-methylbenzazepines synthesized by this procedure. Other 3-alkyl-7,8-dimethoxy precursors of compounds **10e–h** listed in Table I were prepared by alkylation of **8a** with the following reagents: R = Et, C_2H_5Br (excess), KOH (4 equiv), MeOH, 8 h, 135 °C (bomb) (100% yield); R = CH_2CH_2OH, $BrCH_2CH_2OH$ (1.5 equiv), K_2CO_3 (4 equiv), DMF, 145 °C, 8 h (88% yield); R = Pr, C_3H_7Br (1.5 equiv), K_2CO_3 (4 equiv), DMF, reflux, 1 h (85% yield); R = Bu, C_4H_9Br (1.5 equiv), K_2CO_3 (4 equiv), DMF, reflux, 1 h (83% yield). The above compounds were checked by the usual parameters and were usually used without further purification for the BBr_3 cleavage reaction. If necessary, the 3-alkyl derivatives were passed through a silica column with

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a 1 to 4% of MeOH in CH_2Cl_2 gradient.

3-Allyl-6-chloro-7,8-dimethoxy-1-(3-methylphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9e). A mixture of 3 g (9 mmol) of **8c**, 5.5 g (40 mmol) of K_2CO_3, and 1.2 g (10 mmol) of allyl bromide in 100 mL of dry DMF was heated at 120 °C (oil bath temperature) for 2 h under N_2. The DMF was evaporated, the residue was partitioned between H_2O and EtOAc, and the EtOAc was washed with H_2O, dried, and concentrated to 2.2 g (66%) of **9e**, which was homogeneous on TLC (R_f 0.88 with 5% MeOH in CH_2Cl_2). A hydrochloride salt was prepared with ethereal HCl. The other 3-allyl derivatives listed in Table II were prepared by this method.

6-Chloro-7,8-dimethoxy-3-(2-furanylmethyl)-1-(3-methylphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (9f). A mixture of 0.7 g (2.1 mmol) of **8c**, 0.69 g (3.3 mmol) of the white, crystalline *N*-hydroxysuccinimide ester of 2-furoic acid (prepared with DCC in THF), 0.5 g of $NaHCO_3$, 5 mL of H_2O, and 2.0 mL of 2-methoxyethanol was stirred for 4 h at 25 °C. Brine was added, and the product was extracted into CH_2Cl_2 to give 4 g of the crude syrupy 3-(2-furanyl) amide. This was chromatographed on 125 g of silica gel with a gradient of 20 to 33% of EtOAc in cyclohexane. The homogeneous fractions (3.31 g, 86%) (R_f 0.45 on TLC with 3:2 cyclohexane/EtOAc) gave the expected IR and NMR spectra. The amide (0.8 g, 1.9 mmol) was dissolved in 20 mL of dry THF and cooled to −15 °C, and BH_3 (6 mmol) in THF (from a solution 1 M in BH_3) was added dropwise. Then the mixture was stirred at 25 °C for 3 h and recooled, and excess MeOH was added cautiously. The solvents were evaporated, and the residue was treated with ethereal HCl to give **9f** (Table II).

6-Chloro-7,8-dihydroxy-3-(2-furanylmethyl)-1-(3-methylphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (11k). Compound **8c** was converted to the 3-(2-furanyl) amide as described for **9f**. A solution of 3.3 g (7.8 mmol) of this amide was dissolved in 50 mL of dry CH_2Cl_2 and cooled to −15 °C. Then 6.5 g (2.6 mmol) of BBr_3 (32.6 mmol of a solution of 1 g of BBr_3 per 5 mL of CH_2Cl_2) was added dropwise, cooling was stopped, and the mixture was stirred at 25 °C for 1 h. Excess MeOH was added cautiously at 0 °C, the solvents were evaporated, the solid (3.1 g) was homogeneous on TLC (R_f 0.27 with 3:2 cyclohexane/EtOAc) and exhibited the proper NMR spectra, and field-desorption mass spectra gave a molecular weight of 397. The crude 7,8-dihydroxy amide was dissolved in 40 mL of dry THF, 2.0 mmol of BH_3 (1 M in THF) was added, and the procedure described for **9f** was followed. The crude **11k** was digested with 50 mL of 3 N HCl at 50 °C for 30 min, evaporated in vacuo, and azeotroped with EtOH to give the white solid hydrochloride of **11k** (1.86 g, 51%). Compound **10n** (Table I) was prepared by essentially the same conditions used for **11k**, except that the solid *N*-hydroxysuccinimide ester of 2-thiophenecarboxylic acid was employed. Compounds **10y** and **10m** were prepared by the procedure used for **11k**.

6-Chloro-7,8-dihydroxy-3-(4-methoxybenzoyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (10p). A solution of 4 g (0.011 mol) of **10a**, 2.6 g (0.015 mol) of 4-methoxybenzoyl chloride, 3.7 g (0.044 mol) of $NaHCO_3$, and 100 mL of 50% aqueous acetone was stirred overnight at 25 °C. The acetone was evaporated, the aqueous residue was extracted with EtOAc, and the extracts were washed with a 5% $NaHCO_3$ solution and H_2O. The crude, concentrated product was crystallized from MeOH to give 3.73 g (80%) of **10p**. Compound **10r** (Table I) was prepared by this procedure in 63% yield.

6-Chloro-7,8-dihydroxy-3-(4-methoxybenzyl)-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (10q). To a solution of 21 mL of 1 M BH_3 in THF was added a solution of 2.2 g (5.2 mmol) of **10p** in 110 mL of dry THF. The resulting solution was refluxed for 2 h, excess MeOH was added to the cooled mixture, and the solvents were evaporated. The residue was dissolved in 30 mL of MeOH and 30 mL of 6 N HCl and refluxed gently for 30 min. The solvents were evaporated, and the residue was azeotroped with EtOH to provide a white solid. A crystallization from MeOH gave 1.5 g (65%) of the hydrochloride salt of **10q**. Compound **10s** was prepared by this procedure in 69% yield (see Table I).

6-Chloro-7,8-dihydroxy-1-(3-hydroxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (10t). A mixture of 1.7 g (4.7 mmol) of **7a** and 2.5 mL of a 48% HBr solution was heated in an oil bath held at 135 °C for 3 h under N_2. The reaction was diluted with 2 volumes of H_2O and evaporated to a dark foam. This was dissolved in MeOH, treated with activated charcoal, filtered, and concentrated to a pale yellow syrup. This was dissolved in CH_3CN and added to ether to give a nearly white hygroscopic solid. After the solid was dried at 65 °C (1 mm), the white powdery hydrobromide salt of **10t** was obtained (1.2 g, 66%). In Table I are listed other compounds prepared by cyclization/demethylation of the amino alcohols **7** to the 7,8-dihydroxy-3-benzazepines **10** and **11**. Other compounds prepared by this method are **10u,v,z** and **11a,e–g,l**.

1-(3-Bromo-4-hydroxyphenyl)-6-chloro-7,8-dihydroxy-2,3,4,5-tetrahydro-1*H*-3-benzazepine (11d). To an ice-cold solution of 12.5 g (0.029 mol) of **7g** in 150 mL of dry CH_2Cl_2 was added dropwise 184 mL (0.146 mol) of BBr_3 in CH_2Cl_2 (from a solution of 1 g/5 mL). An initial greenish precipitate gradually dissolved as the solution was being stirred at 25 °C for 18 h. The mixture was recooled, excess MeOH was added, and the solvents were evaporated and azeotroped with MeOH to afford a tannish solid. This was suspended in hot MeCN, and MeOH was added to complete the solution. About one-half of the solvent was evaporated in vacuo to incipient crystallization, the mixture was chilled to −30 °C, and the beige crystals were filtered and washed with cold MeCN to give 9.1 g (67%) of the hydrobromide salt of **11d**. Other compounds prepared by BBr_3 demethylation are found in Table I and include **10c,e–j,w,x** and **11b,h,j**.

3-(Trifluoromethyl)-α-[[(2-chloro-3,4-dimethoxyphenethyl)amino]methyl]benzyl Methyl Ether (13). A mixture of 8.4 g (0.039 mol) of **6**, 11.0 g (0.039 mol) of **12**,[14] 5.6 g (0.04 mol) of K_2CO_3, and 30 mL of toluene was heated at 105 °C and stirred for 3 h. The reaction partially solidified. After cooling, the residue was partitioned between a 5% $NaHCO_3$ solution and EtOAc. The EtOAc layer was washed with brine, dried, and concentrated to about 20 g of an oil. This was chromatographed on 500 g of silica gel with 1 to 2% of MeOH in CH_2Cl_2. The homogeneous fractions (TLC with CH_2Cl_2/MeOH, 9:1, gave an R_f of 0.76) were dissolved in ether and acidified with ethereal HCl to give a solid, which was crystallized from MeCN to afford 5.5 g (31%) of the hydrochloride salt of **13**, mp 200–202 °C. Anal. ($C_{20}H_{23}ClF_3NO_3$·HCl) C, H, N.

6-Chloro-7,8-dihydroxy-3-methyl-1-[3-(trifluoromethyl)-phenyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (11m). A solution of 3.6 g (8.6 mmol) of the free base **13**, 20 mL of 37% HCHO, and 26 mL of 88% HCOOH was heated on the steam bath for 5 h, diluted with ice, basified with 10% NaOH solution, and extracted with EtOAc. The washed and dried residual oil **14** was dissolved in 25 mL of HOAc and 50 mL of 48% HBr solution and heated in an oil bath held at 125 °C for 5 h under N_2. The cooled mixture was diluted with MeOH, treated with activated charcoal, and evaporated to an amber residue. This was triturated with MeCN to provide 510 mg (13%) of the hydrobromide salt of **11m**. An analytical sample was prepared from absolute EtOH, mp 264–266 °C.

6-Chloro-7,8-diacetoxy-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (10b). To a suspension of 2.5 g (8.7 mmol) of **10a** in 50 mL of CF_3COOH was added 3.2 g (26 mmol) of acetyl bromide, and the mixture was refluxed for 2 h as **10a** dissolved. The solvent was evaporated, and the residue was partitioned between cold $NaHCO_3$ solution and ether. The ether layer was washed with $NaHCO_3$ solution and brine, and the dried concentrated product was acidified with ethereal HCl. The white precipitate was recrystallized from MeOH–ether to give 1.7 g (48%) of the hydrochloride salt of **10b**. Compounds **10d** and **10l** were also prepared by this procedure.

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