organic chemist that polymers of the type of Figure 10 could be potent toxins and carcinogens, as well as potential DNA-binding antitumor drugs. Synthetic investigations of this class of molecule (T. Smith, private communication) are under way in this laboratory.

Acknowledgment. We thank Mary Kopka, Phil Pjura, Chun Yoon, and Gil Privé for stimulating discussions on groove-binding by netropsin, Hoechst 33258, bleomycin, and other antibiotics and for suggestions and criticisms of the DNA groove-fitting concept. We also thank Peter Dervan for information about distamycin binding in advance of publication. This work was supported by NIH Grant GM-31299. D.G. is the holder of a predoctoral traineeship under USPHS National Research Service Award GM-07104.

Dopamine Receptor Agonists: 3-Allyl-6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol and a Series of Related 3-Benzazepines

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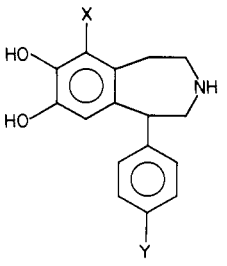
The *N*-allyl derivative (SK&F 85174) of 6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol (SK&F 82526) not only retains the exceptional D-1 agonist potency of its parent but also displays reasonably potent D-2 agonist activity, as measured by a dopamine-sensitive adenylate cyclase test and a rabbit ear artery assay, respectively. Several additional N-substituted compounds were prepared to explore the D-2/D-1 agonist relationship. The *N*-methyl analogue retained good D-2 agonist potency, but this substitution converted D-1 agonist activity into antagonist activity. Most other N-substituents sharply decreased D-2 agonist potency including the *N*-*n*-propyl group. This observation was surprising since the introduction of mono- or di-*N*-*n*-propyl substituent(s) is commonly linked with retention or enhancement of D-2 agonist potency in other series of dopamine agonists. The *N*-(2-hydroxyethyl) analogue retains about one-fourth the D-2 potency of SK&F 85174. Several synthetic methods were used to prepare these compounds. N-Allylation of a trimethoxybenzazepine followed by cleavage of the methyl ethers with boron tribromide was the preferred method. Other methods used were direct alkylation of the trihydroxy secondary amine, i.e., SK&F 82526, and an acylation–amide reduction–cleavage method.

Research into the nature of dopamine receptors has provided substantial understanding of the role they play in various physiological states.[1,2] In particular, the classification of dopamine receptors into D-1 and D-2 subtypes by Kebabian and Calne[3] has stimulated development of specific biological tests for agents acting selectively at these receptor subtypes and has enabled subsequent development of pharmacological methodology to show the whole animal effects of selectively stimulating the D-1 and D-2 receptors, centrally and peripherally.[4]

Setler et al.[5] have reported on the central effects of SK&F 38393 (1), a D-1 agonist with some mixed antagonist effects, and identified it as a potential antiparkinsonism agent.



1. X = Y = H
2. X = Cl; Y = OH

In more recent research, attention has been focused on the effects of D-1 and D-2 agonists on the cardiovascular and the renal systems, particularly the renal vasculature. SK&F 82526 (2) has been shown by Weinstock et al.[6] and Hahn et al.[7] to be a potent and selective D-1 agonist acting primarily peripherally and exerting its effects largely on the kidney vasculature by causing potent vasodilation and increases in renal blood flow. Stote et al.[8] have confirmed these pharmacological findings by clinical experimentation.

Stimulation of D-2 receptors located presynaptically on postganglionic sympathetic neurons would inhibit the amount of neuronally released NE per nerve impulse. Agents acting by this mechanism could be expected to be of therapeutic utility in disease states such as angina pectoris and hypertension where increased sympathetic activity leading to elevated NE levels is believed to play a key role.[1,4,9,10]

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[‡] Pharmacology Department.
[§] Molecular Pharmacology Department.

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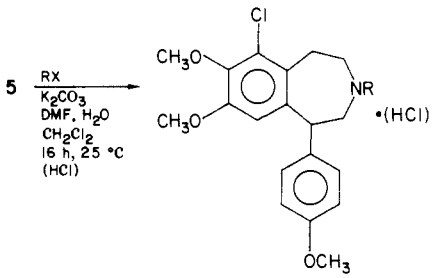
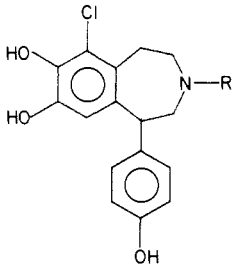
Table I. Trimethoxy Tertiary Amines



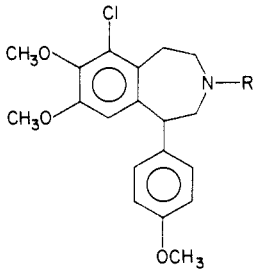
compd	RX	yield, %	R	salt (base)	mp, °C	recrystn solvent
6	$BrCH_2CH{=}CH_2$	90	$CH_2CH{=}CH_2$	base	88–90	hexane
12	*a*	75	CH_3	base	oil	
13	$BrCH_2C{\equiv}CH$	76	$CH_2C{\equiv}CH$	HCl	206–207	EtOH
14		46	CH_2CH_2OH	base	oil	
15	*b*	62		HCl	176–177	$EtOH/Et_2O$

[a] Trimethoxy secondary amine **5** was acylated by reflux with excess ethyl formate for 2 h and the resulting formamide, an oil, was reduced with borane/THF to give the tertiary amine in 75% overall yield, isolated as an oily free base by extraction with ethyl acetate. [b] Trimethoxy secondary amine **5** was acylated with cyclopropanecarboxylic acid chloride to give the corresponding amide in 75% yield, mp 124.5–125.5 °C. This was reduced with borane/THF to give the tertiary amine in 82% yield, isolated as the hydrochloride salt.

Further work on compounds related to **2** has disclosed that D-2 agonist effects may be extended to this series of compounds and potent D-1 agonist effects retained as well. The lead compound among this subgroup is SK&F 85174 (**3**), the *N*-allyl derivative of **2**. Pharmacological reports by Hahn et al.[7] and Blumberg et al.[11] characterized the pre- and postsynaptic dopamine agonist activities of this compound.



3. R = $CH_2CH{=}CH_2$
7. R = $CH_2CHOHCH_2OH$

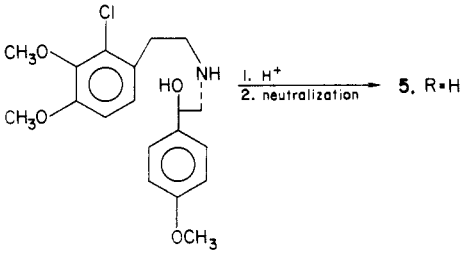


5. R = H
6. R = $CH_2CH{=}CH_2$

A number of analogues of **3** have been prepared to further explore the structural requirements for combining D-2 and D-1 agonist effects in the same molecule. This paper primarily reports on the effects of altering the N-substituent.[12]

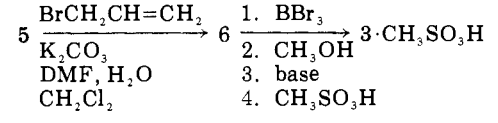
In this study the *N*-allyl group was found to be uniquely effective in conferring D-2 agonist effects on the 3-benzazepine nucleus while retaining the D-1 agonist activity of the parent secondary amine. Other closely related N-substituted analogues were generally less potent than **3** in tests both for D-2 agonism as well as D-1 agonism. These included the *N*-*n*-propyl compound **22**. The *N*-methyl analogue **16** did show D-2 agonist activity comparable to **3**, but this substituent converted D-1 agonist activity to antagonist activity.

Chemistry. A number of routes may be employed to synthesize the amino carbinol **4**, which is then cyclized under acidic conditions to give the trimethoxybenzazepine **5** in high yield. Some of this chemistry has been described in an earlier communication in this journal.[6]

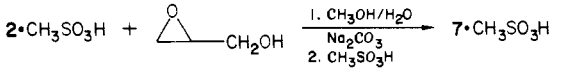


4

Alkylation of **5** with allyl bromide to afford **6**, followed by methoxyl cleavage, provides **3**.



This is the preferred method for preparing **3** and analogous tertiary amines. Direct alkylation of the trihydroxy compound may also be employed, and this method was utilized for preparation of several of the analogues where the acidic nature of the ether cleavage reaction was judged to be detrimental to the stability of the final product. The "direct" alkylation approach yields a less pure product, however, and the tedious purification techniques required to prepare a satisfactorily pure final product contribute to the low observed yields. This process is illustrated for **7**.



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(10) The search for potent and selective D-2 agonists has resulted in the discovery in our laboratories of the most potent D-2 agonist described to date, 4-[(di-*n*-propylamino)ethyl]-7-hydroxyoxindole, SK&F 89124, which has an EC_{50} of 2 nM in our standard D-2 assay (see Table IV): Huffman, W. F.; Hall, R. F.; Grant, J. A.; Wilson, J. W.; Hieble, J. P.; Hahn, R. A. *J. Med. Chem.* **1983**, *26*, 933–935.

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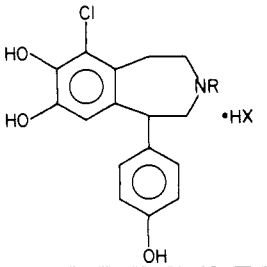
(12) A preliminary report on this work was presented at the 187th National Meeting of the American Chemical Society, St. Louis, MO, April 8–13, 1984.

Table II. Trihydroxy Tertiary Amines



compd	reaction	R	yield, %	salt	mp, °C	recrystn solvent
3	a	$CH_2CH=CH_2$	89	CH_3SO_3H	254–255 dec	MeOH–MeCN–Et_2O
7	b	$CH_2CHOHCH_2OH$ (glycidol)	20	$CH_3SO_3H\cdot 0.75H_2O$	152–157	MeOH–EtOAc (diastereomers)
16	a	CH_3	70	HBr	276–278 dec	MeOH–MeCN
17	a	$CH_2C\equiv CH$	58	$CH_3SO_3H\cdot 0.75H_2O$	>156 dec	*i*-PrOH–Et_2O, MeOH–Et_2O
18	a	CH_2CH_2OH	27	HCl	233–237	MeOH–Et_2O
19	a		62	$HBr\cdot 1.0H_2O$	dec >220	*i*-PrOH–Et_2O
20	b	(*E*)-$CH_2CH=CHCH_3$ ($ClCH_2CH=CHCH_3$)	20	base	202–204	*i*-PrOH–hexane
21	b	(*E*)-$CH_2CH=CHC_6H_5$) ($ClCH_2CH=CHC_6H_5$)	32	base	223–224	MeOH–MeCN
22	c	*n*-C_3H_7	80	CH_3SO_3H	236–237.5	MeOH–MeCN

[a] Compound prepared by boron tribromide demethylation of corresponding trimethoxy tertiary amine. [b] Compound prepared by direct alkylation of the trihydroxy secondary amine **2**. Reagents are indicated in parentheses. [c] This compound was prepared by catalytic reduction of the *N*-allyl trihydroxy compound **3** in ethanol with use of palladium-on-carbon catalyst.

Table I shows intermediate tertiary amino trimethoxy compounds typically prepared by N-alkylation. Table II shows final-product compounds, prepared either by direct alkylation of **2** or by the two-step process.

An isomer of **3** in which the hydroxyl group at the 4-position of the 1-aryl substituent is moved to the 3-position was also prepared. The synthesis of this compound (**11**) was as shown in Scheme I.

Biology. Evaluation of D-2 agonist potency was carried out in an isolated perfused rabbit ear artery preparation as described by Hieble and Pendleton[13a] and Steinsland and Hieble.[13b] In this preparation constrictor response to electrical field stimulation is measured in the presence of increasing concentrations of the test compound. That the observed inhibition occurred through a D-2 process (inhibition of NE release) as opposed to a direct α-antagonist effect was determined for several compounds by measurement of [^{3}H]NE release.

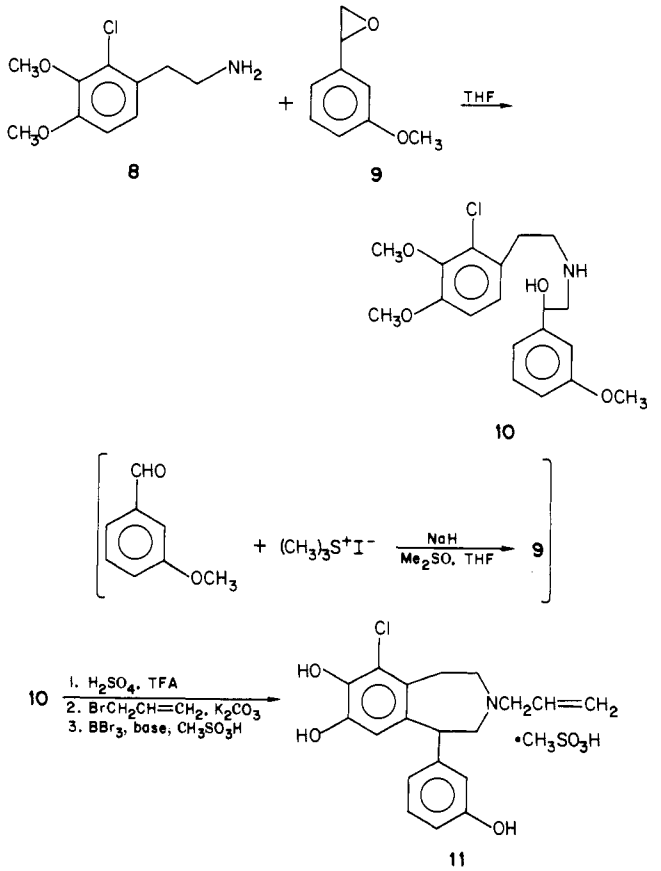
Evaluation of D-1 agonist potency was accomplished in a dopamine-sensitive adenylate cyclase preparation as described by Setler et al.[5] In this preparation the stimulation of cyclic AMP production in homogenates of rat striatum is determined in the presence of increasing concentrations of test compound. Effects of **3** and the related compounds prepared in this study are shown in Table III.

Results and Discussion

Studies by Kaiser et al.[14] have shown that both D-1 and D-2 agonist activities reside virtually entirely in the *R* enantiomer of **3**. Further, the *S* enantiomer of **3** does not show dopamine antagonist activity. Except for **3**, none of the compounds reported in this study has been resolved.

In a comparison of racemic compounds, **3** is ca. 8 times as potent a D-2 agonist as **2** and it is also 3–4 times more potent as the secondary amine as a D-1 agonist. The *N*-methyl compound **16** is slightly more potent than **3** as a D-2 agonist but shows primarily antagonist effects in the adenylate cyclase assay. The *n*-propyl compound **22** is only weakly active as a D-2 agonist. This is surprising since *N*-*n*-propyl or *N*,*N*-di-*n*-propyl substitution commonly maintains or enhances D-2 potency in other series of compounds showing D-2 agonist activity. This is true for

Scheme I



(13) (a) Hieble, J. P.; Pendleton, R. G. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1979**, *309*, 217–224. (b) Steinsland, O. S.; Hieble, J. P. *Science* **1978**, *199*, 443–445.

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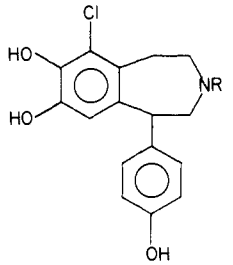
Table III. Dopamine Agonist Activity



compd	R	salt	rabbit ear artery:[a] EC_{50}, nM	dopamine-sensitive adenylate cyclase:[b] EC_{50}, nM
3	$CH_2CH=CH_2$	CH_3SO_3H	122[c]	15 (80)[d]
(*R*)-3	$CH_2CH=CH_2$	CH_3SO_3H	84[c]	9 (80)
(*S*)-3	$CH_2CH=CH_2$	CH_3SO_3H	3000[c]	>10000
22	n-C_3H_7	CH_3SO_3H	1000	550 (80)
16	CH_3	HBr	90	~10000 (30)[e]
17	$CH_2C\equiv CH$	CH_3SO_3H	2700	640 (42)
19		HBr	1700	1100 (35)
18	CH_2CH_2OH	HCl	500	1000 (23)
7	$CH_2CHOHCH_2OH$	CH_3SO_3H	>10000	nt[f]
20	(*E*)-$CH_2CH=CHCH_3$	(base)	10000	nt
21	(*E*)-$CH_2CH=CHC_6H_5$	(base)	inact	nt
11	$CH_2CH=CH_2$[g]	CH_3SO_3H	760	125 (70)
2	H	CH_3SO_3H	1000[c]	57 (70)

[a] Nanomolar concentration of compound necessary to inhibit 50% of the constrictor response (increase in perfusion pressure) to electrical stimulation. [b] Nanomolar concentration of compound necessary to cause a 50% increase in cAMP formation relative to the maximum increase caused by this compound over the range of concentrations tested. [c] Inhibition of release of NE confirmed by assay. [d] Figure in parentheses shows maximum response. [e] This compound showed mixed agonist/antagonist activity in this assay, the latter effect predominating. Antagonist IC_{50} = 600 nM. [f] nt = not tested. [g] Hydroxyl in 1-phenyl substituent moved from the 4′- to 3′-position.

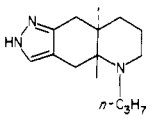
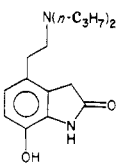
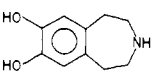
N,*N*-dialkyldopamines,[9] *N*-*n*-alkylapomorphines,[16] the oxindole series of D-2 agonists typified by SK&F 89124,[10] and the pyrazolodecahydroquinolines typified by LY 141865.[17] For comparison of D-2 agonist potency of **3** with other compounds studied as dopamine agonists, see Table IV. *N*-Allyl substitution seems to be uniquely effective in the 3-benzazepine series of dopamine agonists. In other series in which *N*-allyl has been included, dopamine agonist activity of these analogues (specifically D-2 agonist activity) has been unimpressive.

Compounds with other N-substituents show significantly lower potencies in the rabbit ear artery (D-2) assay, our primary test. The propargyl and cyclopropylmethyl analogues **17** and **19** are much weaker than **3** while the 2-hydroxyethyl analogue **18** has roughly one-fourth the potency of **3**. A 2,3-dihydroxypropyl analogue **7** (stereoisomerism undetermined) is inactive as are compounds bearing 3-methyl- or 3-phenyl substituents on the *N*-allyl group (predominately *E* stereochemistry). An isomer of **3** in which the hydroxyl group in the 1-aryl substituent is moved from position 4′ to 3′, i.e., **11**, is about one-sixth as potent as the parent. Data for **2** are included in Table III for comparative purposes.

The combination of D-1 and D-2 agonist activities displayed by **3** should result in the overall pharmacological response of hypotension in a whole animal evaluation.[1] Stimulating D-1 receptors results in vasodilation, principally in the renal vasculature. Stimulating D-2 receptors attenuates the release of norepinephrine through a feedback mechanism which will generally relax vascular tone, also resulting in a vasodilator effect. The additive vasodilator effects predict hypotensive activity,[9] an effect that is observed pharmacologically.[11a-c]

Efforts to develop a structural hypothesis to explain the "allyl effect" and place these compounds in a model relating dopamine agonist effects to those of other established series of dopamine agonists have not been particularly productive. ^1H NMR studies (particularly high-field ones) have established that **3** displays at least two stable conformers in solution.[15] The temptation to simplistically relate each conformer to a specific form of dopamine

Table IV. Standard D-2 Receptor Agonists

compd	struct	REA:[a] EC_{50}, nM
dopamine		38
N,*N*-di-*n*-propyldopamine		60
N-*n*-Butyl-*N*-*n*-propyldopamine		48
apomorphine		44
6,7-ADTN		17
LY 141865		108
SK&F 89124-A		2
SK&F 39315-A		12
3		122

[a] Rabbit ear artery assay. For description of this test, see the Experimental Section.

(15) De Brosse, C., Smith, Kline and French Laboratories, personal communication.
(16) Cannon, J. G. "Peripheral Dopamine Receptors, Advances in the Biosciences"; Imbs, J. L., Schwartz, J., Eds.; Pergamon Press: New York, 1978; Vol. 20, pp 87–94.
(17) Bach, N. J.; Kornfeld, E. C.; Jones, N. D.; Chaney, M. O.; Dorman, D. E.; Paschal, J. W.; Clemens, J. A.; Smalstig, E. B. *J. Med. Chem.* **1980**, *23*, 481–491.

agonist activity was quickly discouraged since many of the analogues described in this paper showed similar conformational effects even though several had essentially no dopamine agonist activity, either D-1 or D-2. At this point perhaps the only conclusion that might be reached regarding a structure–dopamine agonist activity hypothesis is that the 1-aryl-3-benzazepines are a new class of dopamine agonist with properties uniquely different from those of other known classes.

Experimental Section

Melting points below 200 °C were determined on a Thomas-Hoover apparatus; melting points above 200 °C were determined in capillary tubes in a heated block (Mel Temp). All are uncorrected. Elemental analyses were determined by the Analytical, Physical and Structural Chemistry Section of Smith Kline & French Laboratories. IR spectra of solids were determined as 1% dispersions in KBr disks while liquids were cast as neat films on KBr or NaCl plates and spectra measured on a Perkin-Elmer Model 683 IR spectrophotometer. ^{1}H NMR spectra were determined on a Varian EM390 90 MHz spectrometer. Gas chromatography (GLC) analyses were carried out on a Perkin Elmer model 3900 instrument using a 4-ft glass packed (3% OV 17) column isothermally at 275 °C.

Chemistry. 3-Allyl-6-chloro-7,8-dimethoxy-1-(4-methoxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (6). A 62.75-g (0.181 mol) quantity of **5**[6] (recrystallized from toluene, mp 142–144 °C) and 24.92 g (0.181 mol) of powdered K_2CO_3 were stirred in a mixture of 300 mL of DMF and 12.6 mL of H_2O. After the amine had dissolved, a solution of 21.85 g (15.62 mL, 0.181 mol) of allyl bromide in 150 mL of CH_2Cl_2 was added dropwise over a period of 5 h.

The reaction mixture was stirred at ambient temperature for 16 h and diluted with 2.5 L of water and extracted three times with CH_2Cl_2. The combined extracts were extracted once with brine, and the CH_2Cl_2 solution was concentrated on a rotary evaporator. The residual oil was taken up in Et_2O, and Et_2O solution was washed successively with water and brine and dried over $MgSO_4$. The solution was filtered and concentrated to an oil, which crystallized on standing. The solid was recrystallized from hexane to give 62.81 g (90%) of **6**, mp 88–90 °C. Anal. ($C_{22}H_{26}ClNO_3$) C, H, N.

3-Allyl-6-chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol Methanesulfonate (3·CH_3SO_3H). A 76.45-g (0.197 mol) quantity of trimethoxy compound **6** was dissolved in 1.6 L of sieve-dried CH_2Cl_2 and the solution stirred under nitrogen and chilled to 3 °C. A solution of 186.6 g (70.7 mL, 0.745 mol) of boron tribromide in 475 mL of sieve-dried CH_2Cl_2 was added dropwise over a period of about 1.75 h while the temperature was maintained at 0–5 °C. The ice bath was removed and stirring continued for about 1.75 h during which time the temperature reached ambient.

The reaction mixture was warmed and concentrated to a small volume by distillation of CH_2Cl_2 in vacuo, and the concentrated solution was chilled in an ice bath. MeOH (about 2 L) was then added dropwise (exotherm). During the late stages of CH_3OH addition the rate of addition was increased and the ice bath removed. The solution was refluxed overnight and then it was concentrated to a dark oil. The oil was stirred with 2 L of H_2O and the mixture treated with 50% NaOH to a pH of 12.5 (meter), giving a clear solution. The pH was then lowered to 7.7 with aqueous HCl, yielding a heavy yellow-green precipitate. This solid was filtered and washed with water. The pH of the filtrate was 6.0 and was adjusted to 8.1 with aqueous NaOH, yielding a second crop of precipitate which was combined with the first crop and the solid dried at 55 °C overnight at atmospheric pressure to give 70.7 g of **3** base. This solid was dissolved in 600 mL of MeOH and a slight excess of methanesulfonic acid was added. The solution was concentrated by boiling and diluted with MeCN. The total volume was reduced to about 1 L by boiling, and the mixture was cooled and diluted with Et_2O. The crystalline solid was filtered, washed with 1:1:3 MeOH–MeCN–Et_2O and dried to give 77.1 g (89%) of **3**·CH_3SO_3H, mp 254–255 °C. Anal. ($C_{20}H_{24}ClNO_6S$) C, H, N. ^{1}H NMR ($CDCl_3$, CD_3OD) δ 6.9 (4 H, q, 1-aryl), 6.15 (1 H, br s, H-9), 5.9–5.3 (3 H, m, vinyl), 4.6 (1 H, d, benzylic), 4.3 (6 H, s, active Hs), 3.9–3.1 (8 H, m, methylenes), 2.7 (3 H, s, CH_3SO_3H). Spectra indicate that **3** exists as more than one stable conformer in solution. IR spectrum was judged consistent with structure **3**·CH_3SO_3H.

6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-3-methyl-1*H*-3-benzazepine-7,8-diol Hydrobromide (16·HBr). A 3.47-g (0.010 mol) quantity of **5** was dissolved in 50 mL of ethyl formate and the solution refluxed 2 h. The solution was concentrated under reduced pressure to give a yellow oil. A TLC on silica gel GF using 5% MeOH in $CHCl_3$ showed a single product spot at R_f 0.7. No starting material (R_f 0.3) remained. IR and ^{1}H NMR spectra confirmed that the *N*-formyl derivative had been formed. The oil was dissolved in 20 mL of dry THF and 20 mL of 0.98 M borane–THF was added. The solution was stirred at ambient temperature for 2.5 h, CH_3OH added, and the solution concentrated on a rotary evaporator. The residue was redissolved in CH_3OH, 3 mL of ethereal HCl was added, and the solution was refluxed for 1.5 h. The solution was concentrated on a rotary evaporator and the residual oil was stirred with water. The mixture was made basic and extracted twice with EtOAc, and the combined EtOAc extracts were back-washed twice with brine, dried over Na_2SO_4, and evaporated to give 2.7 g (75%) of a pale yellow oil. TLC (silica gel GF using 5% CH_3OH in $CHCl_3$) showed a single spot at R_f 0.5. No starting *N*-formyl compound (R_f 0.7) remained. The oil (2.7 g, 0.0075 mol) was treated with 6.3 mL (0.067 mol) of BBr_3 in 40 mL of CH_2Cl_2 by using the same procedure as described for compound **3** above. A 2.07-g (70%) quantity of **16**·HBr was obtained as a light pink solid, mp 265–275 °C after recrystallization from MeOH–Et_2O. This was recrystallized from MeOH–MeCN to give material of mp 275–276 °C dec. Anal. ($C_{17}H_{19}BrClNO_3$) C, H, N. IR and ^{1}H NMR spectra were consistent with structure **16**·HBr.

6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-propargyl-3-benzazepine-7,8-diol Methanesulfonate (17·CH_3SO_3H). Secondary amine **5** was alkylated with propargyl bromide with use of the same conditions described for **6** (see preceding procedure). The intermediate was isolated as the hydrochloride (see Table I). Methyl ether cleavage was by the same method as described for compound **3** (see preceding procedure) after treating the hydrochloride with aqueous Na_2CO_3 and extracting the base with CH_2Cl_2. The CH_2Cl_2 solution was dried over $MgSO_4$ and concentrated, and the residual oil was redissolved in dry CH_2Cl_2 for the cleavage reaction. The cleaved product, **17**, as the methanesulfonate salt showed an unusual tendency to solvate during purification attempts. Acetonitrile was particularly difficult to remove. Ultimately *i*-PrOH–Et_2O was found to be a satisfactory recrystallization system (see Table II). Anal. ($C_{20}H_{22}ClNO_6S$·0.75H_2O) C, H, N. IR and ^{1}H NMR spectra were consistent with structure **17**·CH_3SO_3H.

6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-3-(2-hydroxyethyl)-1*H*-3-benzazepine-7,8-diol Hydrochloride (18·HCl). Compound **5** (13.3 g, 0.0383 mol) was dissolved in a mixture of 250 mL of MeOH and 50 mL of CH_2Cl_2 and a 20-mL portion of ethylene oxide (chilled liquid) was added in one portion. The reaction mixture was stirred at ambient temperature for 2 h. A TLC on a silica gel GF plate using 10% MeOH in $CHCl_3$ showed one new spot and indicated no remaining starting material. The solution was concentrated on a rotary evaporator to give a yellow oil in essentially quantitative yield. This material was used without further puirification in the ether cleavage reaction. A 4.14 molar ratio of BBr_3 was used and the reaction and isolation–purification conditions were identical with those described for compound **3** (see preceding procedure) with the exception that this compound was converted to a hydrochloride salt (see Table II). Anal. ($C_{18}H_{21}Cl_2NO_3$) C, H, N. IR and ^{1}H NMR spectra were consistent with structure **18**·HCl.

6-Chloro-3-(cyclopropylmethyl)-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol Hydrobromide (19·HBr). Compound **5** (10.0 g, 0.0288 mol) was dissolved in 200 mL of toluene and a solution of 7.94 g (0.0576 mol) of K_2CO_3 in 400 mL of water was added. To this stirred mixture was added 3.13 g (0.030 mol) of cyclopropanecarboxylic acid chloride in 50 mL of dry toluene. The reaction mixture was stirred for 16 h at ambient temperature. The toluene layer was separated and the aqueous phase reextracted with CH_2Cl_2. The combined extracts were diluted with Et_2O/EtOAc and extracted with 10% aqueous

HCl. The organic phase was dried over $MgSO_4$, filtered, and concentrated on a rotary evaporator to give 12.1 g of an orange-red oil. This was triturated with hexane and a small amount of crystalline material was obtained upon allowing the hexane solution to stand. The residual oil was dissolved in *n*-butyl chloride, and this solution was diluted with hexane to give an oil which slowly crystallized upon seeding. This solid was recrystallized from *n*-butyl chloride–hexane to give two crops of the *N*-cyclopropylcarbonyl derivative of **5**, 8.99 g (75%), mp 124.5–125.5 °C. This material was dissolved in dry THF and 43.1 mL (0.043 mol) of borane–THF was added dropwise without a noticeable exotherm. The solution was then refluxed for 3 h and partly concentrated and 60 mL of MeOH was added dropwise and the resulting solution refluxed for 16 h. After this solution was partly concentrated, Et_2O was added to give a cloudy solution which was filtered and treated with a slight excess of ethereal HCl to give a gummy precipitate which slowly crystallized. The crystalline material was filtered, washed with Et_2O, and recrystallized from EtOH–Et_2O to give **15**·HCl (see Table I). Anal. ($C_{23}H_{29}Cl_2NO_3$) C, H, N.

A 4.88-g (0.0116 mol) portion of base **15** (isolated by treating the hydrochloride with 5% aqueous Na_2CO_3 and extracting into CH_2Cl_2, drying this solution over $MgSO_4$, and concentrating the filtrate to an oil) was dissolved in 100 mL of dry CH_2Cl_2 and treated with 12.48 g (0.0498 mol) of BBr_3 in 40 mL of CH_2Cl_2 as described for the preceding compound. Isolation–purification of the reaction product differed in that the crude product hydrobromide was not converted to the free base but was purified directly by concentrating the MeOH solution to 5.17 g of tan foam. This was crystallized from MeOH–H_2O to give a crop of 2.16 g of crystalline solid which was filtered and the filtrate deposited a gum. The gum was crystallized from *i*-PrOH–Et_2O to give a crop of 1.31 of crystalline solid. Both crops of solid were combined and recrystallized from *i*-PrOH–Et_2O to give 3.16 g (62%) of crystalline product **19**·HBr (see Table II). Anal. ($C_{20}H_{23}BrClNO_3$) C, N, N. IR and ^1H NMR spectra were consistent with structure **19**·HBr.

Direct Alkylation of 2. *trans*-6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-(3-methylallyl)-3-benzazepine-7,8-diol Hydrate (20). A 5.00-g (0.01244 mol) quantity of **2**·CH_3SO_3H was dissolved in 200 mL of DMF and 2.0 mL of H_2O was added. A 5.15-g (0.0373 mol) quantity of K_2CO_3 was added and 1.24 g (0.0137 mol) of (*E*)-1-chloro-2-butene was added as a solution in 20 mL DMF. The reaction mixture was stirred at ambient temperature for 16 h and then poured into aqueous pH 7 buffer to give a solid. This was filtered and dried to give 3.7 g. GLC analysis of the crude product as the BSTFA/MBTFA (*N*,*O*-bis(trimethylsilyl)trifluoroacetamide/*N*-methylbis(trifluoroacetamide)) derivative indicated 13% recovered **2** and 73% of a new product. Attempts to form salts (hydrochloride, methanesulfonate) led to noncrystalline products. The free base was triturated with boiling *i*-PrOH, some insolubles were filtered, and the filtrate was diluted with hexane to give 1.36 g of crystalline solid. GLC analysis (BSTFA/MBTFA derivative) indicated this material was predominately recovered **2**. Concentration of the filtrate and further dilution with hexane gave a second crop of solid, 1.12 g. GLC analysis (above method) showed no starting **2** to be present and the sample to be 70% of one component. This material was recrystallized from *i*-C_3H_2OH–hexane to give 0.89 g of crystalline free base **20**. Anal. ($C_{20}H_{22}ClNO_3$·$0.2H_2O$) C, H, N. IR and ^1H NMR spectra were consistent with structure **20**.

(*E*)-6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-(3-phenylallyl)-3-benzazepine-7,8-diol (21). The method directly preceding was used to prepare this analogue, using *trans*-3-chloro-2-propenylbenzene in the same molar quantity in the same scale reaction. The crude free base was filtered to give 5.34 g of crude product. This material was placed in a Soxhlet extractor and extracted with Et_2O for 16 h. Concentration of the Et_2O extract and dilution with hexane gave 2.58 g of crystalline solid, which was recrystallized from MeOH–MeCN–$CHCl_3$ to give 1.70 g of **21** (see Table II). Anal. ($C_{25}H_{24}ClNO_3$) C, H, N. IR and ^1H NMR spectra were consistent with structure **21**.

6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-3-(2,3-dihydroxypropyl)-1*H*-3-benzazepine-7,8-diol Methanesulfonate (7·CH_3SO_3H). A 10.0-g (0.0249 mol) quantity of **2**·CH_3SO_3H was dissolved in a mixture of 100 mL of MeOH and 20 mL of H_2O by warming to 50–60 °C and 53 mL (0.0249 mol) of 5% aqueous Na_2CO_3 was added in one portion, precipitating the free base of **2**. The mixture was stirred and maintained at 50–60 °C and 2.79 g (0.0375 mol) of glycidol (redistilled before use) was added in one portion and the mixture stirred at reflux for 16 h. The precipitated base completely redissolved after 1–2 h of reflux and the solution remained clear during the remainder of the reflux period but darkened somewhat. The reaction mixture was cooled, acidified with methanesulfonic acid, and concentrated under reduced pressure to give a heavy brown oil. This was taken up in MeOH and MeCN added to precipitate inorganic salts which were filtered. The filtrate was assayed by HPLC using a 4.6 mm × 250 mm Zorbax C-18 reversed phase column using a buffer composed of 59.5% MeOH, 39.5% H_2O, 1% HOAc, and 10^{-5} M sodium octanesulfonate. This assay showed two principal reaction products in ca. 3:1 ratio and no recovered starting material. The filtrate was reconcentrated to a brown oil, which was stirred with EtOAc. The EtOAc supernatant was decanted and the residue was taken up in MeOH, which caused a crystalline solid to form. This was filtered and dried to give 2.5 g (20%) of **7**·CH_3SO_3H (see Table II). Anal. ($C_{20}H_{26}ClNO_8S$·$0.75\ H_2O$) C, H, N. IR and ^1H NMR spectra were consistent with structure **7**·CH_3SO_3H.

6-Chloro-2,3,4,5-tetrahydro-1-(4-hydroxyphenyl)-1*H*-3-*n*-propyl-3-benzazepine-7,8-diol Methanesulfonate (22·CH_3SO_3H). Compound **3**·CH_3SO_3H (6.93 g, (0.0157 mol) was added to 250 mL of EtOH and 30 mL of H_2O containing 150 mg of 5% palladium-on-carbon. The mixture was hydrogenated on a Parr apparatus at ambient temperature. Pressure drop equivalent to 1 mol of hydrogen uptake occurred after ca. 10 min shaking and then ceased. The reaction mixture was filtered and the filtrate concentrated to give a light brown foam. This was dissolved in boiling MeOH and $CHCl_3$ was added in several portions to cause the separation of an oil which crystallized upon cooling with continued stirring. The crystalline solid was filtered and recrystallized from MeOH–MeCN to give 5.5 g (80%) of crystalline solid **22**·CH_3SO_3H (see Table II). Anal. ($C_{20}H_{26}ClNO_6S$). C, H, N. IR and ^1H NMR spectra were consistent with structure **22**·CH_3SO_3H.

3-Allyl-6-chloro-2,3,4,5-tetrahydro-1-(3-hydroxyphenyl)-1*H*-3-benzazepine-7,8-diol Methanesulfonate (11·CH_3SO_3H). 3-Methoxystyrene oxide (**9**)[18] was prepared as follows. A 17.67-g (0.367 mol) quantity of sodium hydride (50% oil dispersion) was washed free of mineral oil with petroleum ether and then it was stirred with 190 mL of sieve-dried Me_2SO under nitrogen. The mixture was heated at 60–65 °C for 2 h during which time there was copious hydrogen evolution. The reaction mixture was cooled, diluted with 175 mL of dry THF, and then was chilled to 3 °C. A solution of 74.9 g (0.367 mol) of trimethylsulfonium iodide in 450 mL of sieve-dried Me_2SO was added dropwise and concurrently with 25.0 g (0.183 mol) *m*-anisaldehyde. The addition required several hours and temperature was held below 5 °C during this period. The reaction mixture was allowed to warm to ambient temperature and then it was stirred overnight. The reaction mixture was diluted with H_2O and was extracted three times with Et_2O, and the combined extracts were washed with brine and dried over $MgSO_4$. The drying agent was filtered and the filtrate concentrated on a rotary evaporator to give an orange oil, 28.93 g. An IR spectrum showed no aldehyde carbonyl. The oil was vacuum distilled to give 12.35 g (45%) of clear liquid **9**, bp (12 torr) 120–122 °C. A ^1H NMR spectrum was consistent with structure **9**.

A 17.54-g (0.0814 mol) quantity of 2-chlorohomoveratrylamine (**8**), which had been isolated from its hydrochloride salt by neutralization with dilute NaOH and extraction into CH_2Cl_2, drying of the extract, and concentration to an oil, was mixed with 12.21 g (0.0814 mol) of 3-methoxystyrene oxide (**9**) in 100 mL of THF. The solution was refluxed 16 h, cooled, and diluted with EtOAc and petroleum ether. Chilling caused crystallization. The solid was filtered, and additional crops were obtained from the filtrate. The crystalline materials were combined and triturated with EtOAc–hexane to give 11.26 g (38%) of *N*-[2-hydroxy-2-(3-methoxyphenyl)ethyl]-2-(2-chloro-3,4-dimethoxyphenyl)ethylamine (**10**), mp 97.5–99 °C.

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The amino alcohol **10** (7.76 g, 0.0212 mol) was dissolved in 35 mL of trifluoroacetic acid, and 1.7 mL (0.032 mol) of concentrated H_2SO_4 was added and the solution refluxed for 3 h. The reaction mixture was poured onto ice and the resulting solution made basic with NH_4OH and extracted three times with CH_2Cl_2. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated on a rotary evaporator to give 6.7 g (91%) of 6-chloro-7,8-dimethoxy-1-(3-methoxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine as an oil. A ^1H NMR spectrum was consistent with this structure.

This compound (5.34 g, 0.0154 mol) was dissolved in 27 mL of DMF and 1.35 mL of H_2O was added, together with 2.12 g (0.0154 mol) of powdered K_2CO_3. A 1.86-g (0.0154 mol) quantity of allyl bromide in 10 mL of CH_2Cl_2 was added dropwise over a 4-h period. The reaction mixture was stirred at ambient temperature during this period and for 6 h following completion of addition. The reaction mixture was poured into H_2O and extracted three times with Et_2O, and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to give a pale green oil, 5.26 g. The oil was dissolved in Et_2O, and the solution was filtered and treated with a slight excess of ethereal HCl to give a gummy precipitate. This was triturated with fresh Et_2O to give a solid which was filtered, washed with Et_2O, recrystallized from MeCN–Et_2O, and dried under vacuum to give 4.44 g (68%) of 3-allyl-6-chloro-7,8-dimethoxy-1-(3-methoxyphenyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine hydrochloride, mp 169–170 °C. Anal. ($C_{22}H_{27}Cl_2NO_3$) C, H, N. A ^1H NMR spectrum was consistent with this structure.

The trimethoxy compound was treated with a 3.77 mol ratio of boron tribromide in methylene chloride in a method exactly analogous to that used for compound **3**. The initially isolated crude hydrobromide was converted to the base and then to the methanesulfonate, which was recrystallized from MeOH–MeCN to give 3.2 g (70%) of **11**·CH_3SO_3H, mp 223–226 °C. Anal. ($C_{20}H_{24}ClNO_6S$) C, H, N. IR and ^1H NMR spectra were consistent with structure **11**-CH_3SO_3H.

Pharmacology. Isolated Perfused Rabbit Ear Artery. A modification of the preparation described by Steinsland et al.[19] was used for these studies; see this reference for a drawing of the perfusion apparatus. Male rabbits weighing from 2 to 3 kg were sacrificed by cervical concussion, and a 2–4-cm portion of the central ear artery was dissected free at the base of the ear, cannulated with polyethylene tubing (Intramedic PE-50) at both ends, and mounted in a perfusion chamber designed to allow simultaneous intraluminal perfusion and extraluminal superfusion of the artery. The chamber itself was formed from a glass tube 125 mm long × 3 mm inside diamter. The major portions of both the intraluminal and extraluminal flows were delivered through small diameter Tygon tubing at a constant rate, usually about 2 mL/min, from two channels of a four-channel peristaltic pump (Buchler/Polystaltic). The perfusate in these two main channels came from a reservoir of Krebs–Henseleit solution. The rate of flow in each of the two other channels of the pump (minor channels) was kept at one-half of the rate in each of the main channels by using for the minor channels tubing with a smaller internal diameter than that used for the main channels. The minor channels were used for the administration of drugs; the flow from these channels could be delivered either extraluminally or intraluminally. The outflow of the extraluminal superfusion was connected to a 90-cm length of tubing, which was elevated to exert an extraluminal pressure of 50 mmHg (70 cm of H_2O) on the artery. The application of this extraluminal pressure improved the stability of the response to nerve stimulation.

The intraluminal inflow perfusion pressure was measured with a Statham P23AA transducer and recorded on a Physiograph (Narco Biosystems). Since the intraluminal flow rate remained constant, changes in perfusion pressure reflected changes in the resistance to flow, i.e., the degree of vasoconstriction. Once an artery was mounted in the chamber, perfusion and superfusion were continued for at least 1 h before an experiment was begun. During this preliminary stabilization period, the sensitivity of the artery to both field stimulation of the sympathetic nerves and administration of vasoconstrictor drugs gradually increased from a low level up to full sensitivity. The sensitivity then remained constant for 10–15 h, provided that the artery was not subjected to excessive intraluminal pressures.

The composition of the Krebs–Henseleit solution was as follows: NaCl, 119 mM; $NaHCO_3$, 25 mM; KCl, 4.7 mM; $MgSO_4$; 1.5 mM; KH_2PO_4, 1.2 mM; glucose, 11 mM; ascorbic acid, 5 μM; disodium EDTA, 30 μM. This solution was gassed with 95% O_2 and 5% CO_2 and maintained at 35 °C. The pH under these conditions was 7.4.

The periarterial sympathetic nerves were excited by field stimulation. Rectangular pulses of 0.7-ms duration and supramaximal voltage (75 V) from an American Electronics Laboratory Model 104A stimulator were delivered through platinum electrodes sealed through the glass at the top and bottom of the perfusion chamber. The nerves were stimulated at 4-min intervals by a train of pulses at 10–15 Hz with a duration of 300–500 ms. To accomplish this automatically, the stimulator was triggered every 4 min by an external device.

All drugs were administered via the extraluminal superfusion. Drugs were given in increasing concentration, each concentration remaining in contact with the tissue for 4 min. The drug concentration was increased immediately following the response of the artery to nerve stimulation.

Adenylate Cyclase. The cAMP formed in caudate homogenates was measured by a modification of the procedures described by Kebabian et al.[20] and Carenzi et al.[21] 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 °C by hand with a Teflon-glass homogenizer in 50 volumes of 50 mM Tris-maleate buffer (pH 7.4) containing 2 mM EGTA. Alliquots (50 μL) of the homogenate were transferred to 250 μL of incubation medium containing 80 mM Tris-maleate buffer (pH 7.4), 2 mM $MgSO_4$, 0.2 mM EGTA, 5 mM aminophylline, 0.05% sodium metabisulfite, and test substances as required. Lastly 20 μL of 10 mM [^{14}C]ATP (final concentration 0.65 mM), ca. 1.5×10^{-6} dpm/sample, was added quickly to all tubes on ice. The reaction was initiated by shaking at 30 °C and incubation continued for 3 min. The reaction was terminated in a boiling water bath for 3 min. Distilled water (600 μL) was added and mixed with each sample.

The [^{14}C]cAMP formed was separated from the [^{14}C]ATP with use of alumina and cation-exchange resin columns as described by Guidotti et al.[22] using the entire sample. The 4-mL cAMP fraction from the Dowex 50 column was collected in scintillation vials, 10 mL of Aquasol II (New England Nuclear) was added, the vials were shaken vigorously to form a gel, and the ^{14}C content was determined by liquid scintillation spectrometry. The cAMP content was calculated with use of the specific activity of the [^{14}C]ATP. The standard deviation of quadruplicate samples was less than 10% of the mean value.

By use of method of least squares, dose–response curves were constructed and EC_{50} and IC_{50} values were calculated. IC_{50} for bulbocapnine and for chlorpromazine is defined as the concentration of antagonist required to reduce the response to the agonist by 50%.

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Registry No. (±)-**2**·CH_3SO_3H, 87900-91-2; (±)-**3**·CH_3SO_3H, 100227-76-7; (*R*)-**3**, 87863-86-3; (*S*)-**3**, 87863-89-6; (±)-**5**, 88764-14-1; (±)-**5**(1-(3-methoxyphenyl deriv.), 100166-79-8; (±)-**5**-(*N*-formyl deriv.), 100166-60-7; (±)-**5**(*N*-cyclopropylcarbonyl deriv.), 100166-63-0; (±)-**6**, 100227-77-8; (±)-**6**·HCl (1-(3-methoxylphenyl

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deriv.), 100166-80-1; (±)-7 (isomer 1)·CH_3SO_3H, 100166-62-9; (±)-7 (isomer 2)·CH_3SO_3H, 100166-82-3; 8, 67287-36-9; (±)-9, 53631-49-5; (±)-10, 100166-64-1; (±)-11·CH_3SO_3H, 100166-66-3; (±)-12, 87863-72-7; (±)-13·HCl, 100166-67-4; (±)-14, 100166-68-5; (±)-15·HCl, 100166-69-6; (±)-16·HBr, 100166-70-9; (±)-17·CH_3SO_3H, 100166-72-1; (±)-18·HCl, 100166-73-2; (±)-19·HBr, 100166-74-3; (±)-20, 100166-75-4; (±)-21, 100166-76-5; (±)-22·CH_3SO_3H, 100166-78-7; 3-$H_3COC_6H_4CHO$, 591-31-1; $(CH_3)_3SI$, 2181-42-2; $BrCH_2CH{=}CH_2$, 106-95-6; $HC{\equiv}CCH_2Br$, 106-96-7; (*E*)-$H_3CCH{=}CHCH_2Cl$, 4894-61-5; (*E*)-$C_6H_5CH{=}CHCH_2Cl$, 21087-29-6; ethylene oxide, 75-21-8; cyclopropanecarboxylic acid chloride, 4023-34-1; (±)-glycidol, 61915-27-3.

Conformational Effects on the Activity of Drugs. 11.[1] Stereostructural Models for the Direct Activation of the α- and β-Adrenergic Receptor[2]

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Two kinds of cyclic analogues of norepinephrine (NE, 7) and isoprenaline (ISO, 8), in which the C(1)–C(2) side chain of these amino alcohols is incorporated in its preferred conformation in the ring of the 2-(3,4-dihydroxyphenyl)-morpholines 9 and 10 (2-DPMs) and in the ring of the 3-(3,4-dihydroxyphenyl)-3-piperidinols 11 and 12 (3-DPPs), respectively, were synthesized and assayed for their adrenergic activity on various isolated preparations. The 2-DPMs and the 3-DPPs showed an α- and β-agonist activity comparable to that of NE and ISO and to that of the *trans*-2-amino-5,6-dihydroxytetrahydronaphthalen-1-ols 13 and 14 (2-ADTNs), which represent another kind of semirigid analogue of NE and ISO. Through a comparison of the stereo structures of the compounds examined and of their pharmacological properties, it was possible to suggest a spatial situation in which the pharmacophoric groups of the adrenergic drugs examined (aryl moiety, amine nitrogen, and alcoholic or ethereal benzylic oxygen) should interact at the receptor site. This spatial situation corresponds to the one found in the preferred conformation of NE and ISO. It was also possible to construct two theoretical three-dimensional molecular models that provide information about steric requirements for the direct activation of α- and β-adrenoceptors, respectively.

The molecular mechanism of the interaction that takes place at the adrenergic receptor has been the subject of extensive work. A number of studies have dealt with the problem of the pharmacophoric conformation and, in particular, with the question of whether the most stable conformation is the one that is "active" at the receptor site. Adrenergic drugs are flexible molecules, and the differences between the ground-state free energies of their conformers are too small to guarantee that no conformational changes take place during the initial process of binding with the receptor. Semirigid cyclic analogues of adrenergic drugs have proved to be a useful tool in studying the conformational aspects of the activity of these drugs at the molecular level, but, although they have yielded some interesting information, they have not made it possible to advance any definite suggestion as to the precise conformation acting at the receptor, because of a residual flexibility. Recently, some rigid analogues have appeared to make a contribution to the solution of this problem.[3,4] It may be pointed out, however, that the steric and electronic effects arising from the additional neighboring atoms necessary to make up the semirigid or rigid structure lead to primary modifications of the physical and chemical properties of the flexible parent compound. This in turn may cause a modification in the biological activity of the pharmacophoric groups in the new molecules compared with the activity elicited by the same groups in the original flexible molecule.[5,6]

Previous papers in this series[5,7-9] have discussed the synthesis and the pharmacological properties of the 1-aryl-2-aminoethanols 1 and 2 and of the corresponding cyclic analogues 3–6. Compounds 3–6 represent two different ways in which the C(1)–C(2) side chain of the amino alcohols 1 and 2 can be locked in a semirigid system. In the morpholine derivatives (3 and 4), the C(1)–C(2) chain is incorporated in the ring through the alcoholic oxygen and the amine nitrogen, which are therefore a part of the ring. In the piperidine derivatives (5 and 6), the C(1) of the side chain is directly engaged in the formation of the ring, and consequently, the alcoholic OH remains free. Both morpholine and piperidine derivatives, either as free bases or as salts, preferentially exist[5,7-9] in the conformations shown in 3, 4 and 5, 6, respectively, with the aryl group in the equatorial position. In both types of cyclic derivatives, the O–C(1)Ar–C(2)–N portion exists in the

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