rats were used in each treatment group, the known standard group, and the vehicle control edema groups. All rats were fasted for 2 h prior to the test and water was available ad libitum. The tested compounds and standard were given orally and were dissolved or suspended in 0.25% methylcellulose. The edema control groups were administered the vehicle. One hour after administration of the test compounds, 0.05 cm^3 of a 1% sterile carrageenan solution was injected into the left hindfoot pad of each rat. Three hours after injection, the paw volumes of the injected paws were measured using a modification of the apparatus described by Adamkiewicz et al.[19] In the primary assay the rate was at 200 mg/kg. ED_{50} values were obtained by using several rates to find the rate which reduced edema formation by at least 25% compared with the mean control in 50% of the rats.

Adjuvant-Induced Polyarthritis Assay.[15] Separate groups of 13 rats were used. For study in the developing arthritic state, compound **4g** was administered orally using methylcellulose as the vehicle beginning on day 1 and once daily thereafter. The dosages studied were 2.5, 5.0, and 10 mg/kg, respectively. On day 2 each animal was injected with 0.5 mL/kg of a 0.5% suspension of heat-killed mycobacterium tuberculosis into the plantar surface of the left paw. Foot volumes were measured on the day of administration of the mycobacterium and again on days 3, 10, and 17. Body weights were recorded daily, and the animals were examined for the spread of the inflammation and the degree of secondary lesions.

For study of the established disease, another group of rats were injected with the mycobacterium and foot volumes were measured. After 20 days of foot volumes were again measured and administration of test compound was begun and continued for 11 days. Foot volume measurements were repeated on day 27 and day 31. The extent of the spread of the inflammation and the degree of lesions were recorded daily, as were the body weights. The effect of compound **4g** was measured by the percentage reduction in the paw volume as compared to the paw volume of the control groups.

LD_{50} Determinations. The LD_{50} values reported in Table III were determined by a standard multidimensional observational assay after the method of Litchfield and Wilcoxon.[20]

Acknowledgment. The research reported in this paper was aided by Industrial Research and Development Incentive Act and subsequent grants. We also thank Dr. R. D. Heilman (G. D. Searle and Co.) for his very helpful comments on the interpretation of the pharmaceutical results.

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α-Adrenergic Agents. 2. Synthesis and α_1-Agonist Activity of 2-Aminotetralins[1,2]

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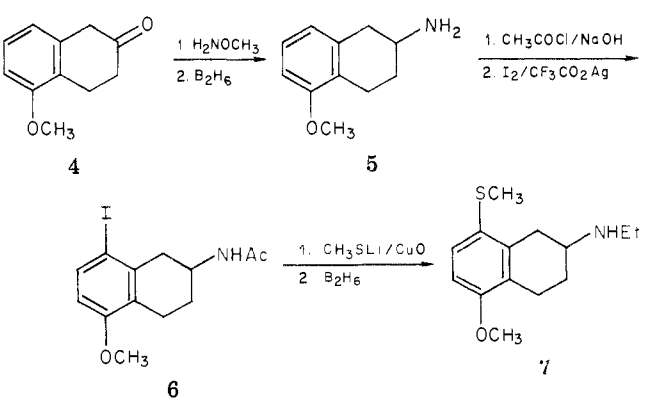
Substituted 2-aminotetralins are potent, selective, direct-acting agonists at postjunctional α_1 receptors. Within this series, substituent alterations on the ring, as well as on the nitrogen, change the potency of compounds by over three orders of magnitude (EC_{50} = 12 to >10 000 nM). It has been demonstrated experimentally that substitution at both the 5 and 8 positions of the aromatic ring produces optimum agonist potency. Removal of either substituent results in a loss of potency and efficacy relative to norepinephrine. Substitution at positions 6 and/or 7 is generally detrimental to activity. Methyl, ethyl, or dimethyl substitution on nitrogen is compatible with high agonist potency, while substitution with larger groups is not. The most potent agonist in this series is 5-(thiomethyl)-8-methoxy-2-aminotetralin, which has an EC_{50} of 12 nM.

In the last decade, a vast amount of research into the structure and function of the adrenergic nervous system has shown unequivocally that the classical α receptor can be subdivided into at least two distinct classes.[3-7] These can be pharmacologically differentiated by their ability to bind with differing affinities a series of agonists and antagonists, as well as by the physiological processes which they regulate. Since the pharmacological characteristics of the peripheral presynaptic receptor are different than those of the classical postsynaptic receptor,[3,7] agonists and antagonists with different activities at both receptor subtypes can be found.[8]

Scheme I



In the peripheral vasculature, there are postjunctional receptors designed as α_1 which mediate vasoconstriction. There are also autoreceptors designated as α_2 which are

(1) This paper has been presented in part. See "Abstracts of Papers", 182nd National Meeting of the American Chemical Society, New York, Aug 23-28, 1981, American Chemical Society, Washington, DC, 1981, Abstr MEDI 13.
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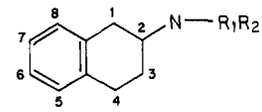
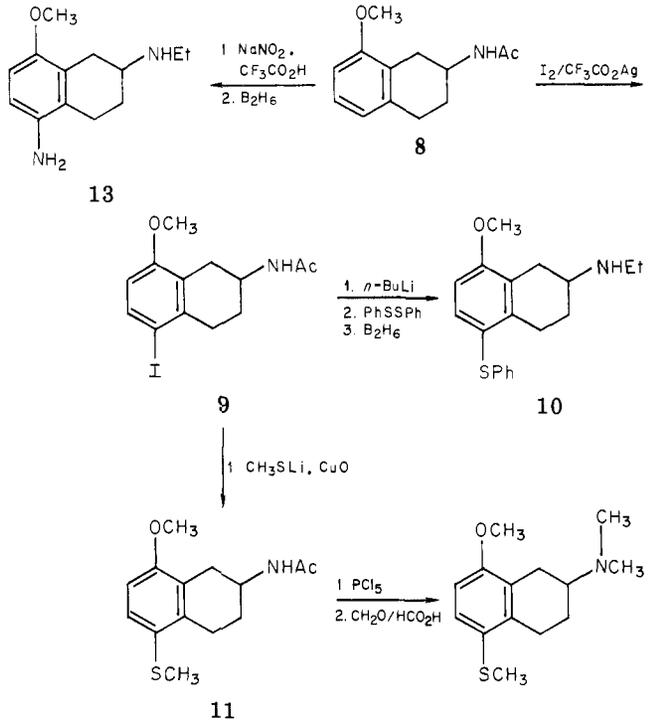
Table I. Structures of Substituted 2-Aminotetralins



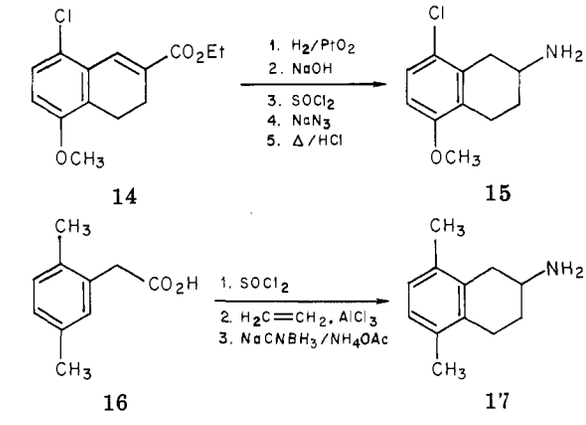
no.	R_1	R_2	position no. 5	6	7	8	mp, °C	formula[a]	anal.
5	H	H	OCH_3	H	H	H	260-264 dec	$C_{11}H_{15}NO \cdot HCl$	C, H, N
7	H	C_2H_5	OCH_3	H	H	SCH_3	208-209	$C_{14}H_{21}NOS \cdot 0.125H_2O$	C, H, N
10	H	C_2H_5	SPh	H	H	OCH_3	226-228	$C_{19}H_{23}NOS \cdot HCl$	C, H, N
12	CH_3	CH_3	SCH_3	H	H	OCH_3	218-219	$C_{14}H_{21}NOS \cdot HCl$	C, H, N
13	H	C_2H_5	NH_2	H	H	OCH_3	>202 dec	$C_{13}H_{20}N_2O \cdot 2HCl \cdot H_2O$	C, H, N
15	H	H	OCH_3	H	H	Cl	235-237 dec	$C_{11}H_{14}ClNO \cdot HCl \cdot 0.75H_2O$	C, H, N
18	H	H	H	H	H	H	241-242[a]	$C_{10}H_{13}N \cdot HCl$	
19	H	H	H	H	H	OCH_3	>275[b]	$C_{11}H_{15}NO \cdot HCl$	C, H, N
20	H	C_2H_5	H	OCH_3	OCH_3	H	256-258	$C_{12}H_{17}NO_2 \cdot HCl$	C, H, N
21	H	H	H	H	OCH_3	OCH_3	212-213	$C_{13}H_{19}NO_2 \cdot HBr$	C, H, N
22	H	H	OCH_3	H	H	OCH_3	265-268[c]	$C_{12}H_{17}NO_2 \cdot HCl$	
23	H	CH_3	OCH_3	H	H	OCH_3	222-224[d]	$C_{13}H_{19}NO_2 \cdot HCl$	
24	CH_3	CH_3	OCH_3	H	H	OCH_3	210[e]	$C_{14}H_{21}NO_2 \cdot HCl$	
25	H	C_2H_5	OCH_3	H	H	OCH_3	185	$C_{14}H_{21}NO_2 \cdot HCl$	C, H, N
26	H	C_3H_7	OCH_3	H	H	OCH_3	265-267	$C_{15}H_{23}NO_2 \cdot HCl$	C, H, N
27	H	C_2H_5	OCH_3	H	H	Cl	255-257 dec	$C_{13}H_{18}ClNO \cdot HCl$	C, H, N
28	H	C_2H_5	OCH_3	H	H	I	>250 dec	$C_{13}H_{18}INO \cdot HCl$	C, H, N
29	H	C_2H_5	I	H	H	OCH_3	260	$C_{13}H_{18}INO \cdot HCl$	C, H, N
30	H	H	SCH_3	H	H	OCH_3	290 dec	$C_{12}H_{17}NOS \cdot HCl \cdot 0.25H_2O$	C, H, N
31	H	C_2H_5	SCH_3	H	H	OCH_3	216-218	$C_{14}H_{21}NOS \cdot HCl$	C, H, N

[a] Literature[18] mp 242-243 °C. [b] Literature[23] mp 273-275 °C. [c] Literature[1] mp 265.5-267.5 °C. [d] Literature[21] mp 222-224 °C. [e] Literature[21] mp 207-208 °C.

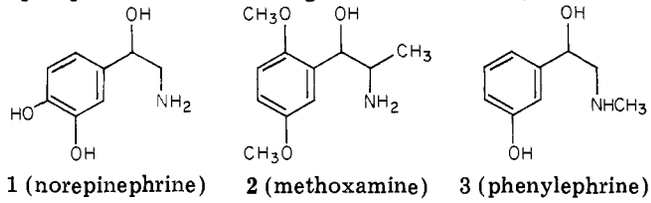
Scheme II



Scheme III



located on the prejunctional terminals of noradrenergic nerves and these serve as an autoregulatory feedback system modulating the release of norepinephrine. Norepinephrine (1), the endogenous transmitter, acts with about equal potency on both pre- and postjunctional α receptors (EC_{50} on $\alpha_1 = 1.5 \times 10^{-7}$ M). Other agents, such as methoxamine (2) or phenylephrine (3), are more selective for the postjunctional α_1 receptor.[2] In a previous paper in this series[2] we described the synthesis and α_1-adrenergic potency of a series of structurally diverse compounds related to the α_1-agonist methoxamine. From among these classes of compounds, the 2-aminotetralins were identified as agents which have particularly interesting properties as α_1-agonists. (For leading articles to the adrenergic properties of 2-aminotetralins, see ref 9–15



1 (norepinephrine) 2 (methoxamine) 3 (phenylephrine)

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(11) B. Costall, R. J. Naylor, J. G. Cannon, and T. Lee, *Eur. J. Pharmacol.*, **41**, 307 (1977).
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and citations therein.) We describe here the synthesis and α_1-agonist activities of a series of substituted 2-aminotetralins.

Chemistry. Previously unreported 2-aminotetralins used in this study were prepared by the general reaction sequences depicted in Schemes I–III. Compounds of known structure were resynthesized by literature methods referenced in Table I, except as noted.

Ketone 4[16] was most efficiently converted to 5-methoxy-2-aminotetralin (**5**) by preparing the *O*-methyloxime and reducing the crude oxime with diborane in THF. Protection of the amino group, followed by iodination with iodine and silver trifluoroacetate, yielded the 8-iodinated amide **6** as the expected major product. Heating this for 3 h in DMF in the presence of cuprous oxide and $LiSCH_3$, followed by reduction of the amide, yielded tetralin **7** (Scheme I). By an analogous sequence, amide **8** was obtained from 8-methoxy-2-tetralone[16] and converted to iodide **9**. While nucleophilic displacement of iodide with thiophenol was not a very efficient reaction, metallation with 2 equiv of *n*-butyllithium, followed by quenching with diphenyl disulfide, introduced the phenylthio. Reduction with diborane gave **10**. Nucleophilic displacement of iodide with thiomethoxide gave **11** from **9**. Hydrolysis under strongly acidic or basic conditions was extremely slow. The amide was hydrolyzed through the imino ester and the amine was methylated under Leuckart conditions to give **12**. Nitration of **8** in trifluoroacetic acid with 1 equiv of sodium nitrite, followed by diborane reduction, yielded **13** (Scheme II).

Unsaturated ester **14** was prepared as previously described.[17] Catalytic reduction, followed by Curtius rearrangement, gave 8-chloro-5-methoxy-2-aminotetralin (**15**) (Scheme III). The dimethylphenylacetic acid **16**[18] was converted to its acid chloride with thionyl chloride. A one-pot acylation/alkylation with ethylene and aluminum chloride gave 5,8-dimethyl-2-tetralone, which was not purified but reductively aminated with sodium cyanoborohydride and ammonium acetate to give 5,8-dimethyl-2-aminotetralin (**17**) (Scheme III).

Results and Discussion

Compounds were tested for their direct α_1-agonist properties as measured by their ability to cause vasoconstriction in the isolated rabbit ear artery, a tissue preparation known to contain postjunctional α_1-receptors. Determination of EC_{50} values was done in the presence of 2×10^{-6} g/mL of cocaine, which is present to block neuronal uptake and rule out an indirect mechanism of action. Further confirmation of a direct mechanism was obtained by running the same determinations in tissues from rabbits which had been pretreated with reserpine to deplete the sympathetic terminals of endogenous norepinephrine. Receptor dissociation constants for phentolamine, a known α antagonist, were determined for most agents and were consistent with an α-adrenergic mechanism. All of the aminotetralins, with the exception of **5**, **10**, and **19**, were full agonists relative to norepinephrine. Unlike norepinephrine, no 2-aminotetralins showed any agonist activity on the prejunctional α_2-receptor in the perfused rabbit ear artery. Activities presented in Tables I–IV are in terms of EC_{50} values relative to norepinephrine the endogenous ligand. Methoxamine, a selective α_1-agonist, is included in all tables for comparison.

It has been shown previously[2] that in the 2-aminotetralin structure the configuration of the nitrogen relative to the aromatic ring is optimum for α_1-receptor agonist activity. The EC_{50} values in Table I illustrate the effects of positional substitution in the aromatic ring of 2-aminotetralins. A completely unsubstituted tetralin, such as **18**, is virtually inactive as an agonist. It is possible in this case that although the nitrogen conformation relative to the aromatic ring may be favorable, the lack of aromatic substitution does not allow sufficient receptor recognition to produce an efficacious ligand–receptor interaction. Addition of a single methoxyl group to either the 5 or 8 position greatly enhances potency, but these compounds are partial agonists. Both compounds produce only about 60% of the maximum response which can be elicited by norepinephrine, the endogenous transmitter. Substitution of both the 5 and 8 positions (compound **22**) with methoxyl groups yields not only a full agonist but one with greater potency than methoxamine (1×10^{-7} vs. 7×10^{-7}). As the data in Table II illustrate, disubstitution at other positions on the ring, such as 6 and 7 or 7 and 8, yields inactive compounds.

The data in Table III shows the effects of nitrogen substitution upon agonist potency. Hydrogen, methyl, or dimethyl substitution of the nitrogen (**22–24**) produces essentially equipotent compounds; all are slightly more potent than methoxamine. Increasing chain length to ethyl (**25**) again increases potency slightly, but this trend falls off rapidly upon further increase to propyl (**26**), which is 25 times less potent than **25**.

The structure–activity data in Table IV show the influences of various substituents in the 5 and 8 positions. With the exception of **17**, which is practically inactive, and **10** (intrinsic activity = 0.8), all are full agonists at the postjunctional α_1 receptor. The values for **7**, **15**, **27**, and **28** indicate that substituents other than methoxyl at position 8 are compatible with high potency. Chlorine is about equipotent with methoxyl, while iodine increases potency only slightly. Variation of the substituents at position 5 had more of an effect for those compounds which were studied (**10**, **12**, **13**, **29**, and **30**). Here, it is noted that structures which have an *S*-methyl at the 5 position (**12**, **30**, and **31**) are very potent agonists. These three compounds are the most potent α_1 agonists which have been identified in this series. The primary amine with a 5-*S*-methyl (**30**) has an EC_{50} of 12 nM and is thus far more potent than methoxamine, phenylephrine, or norepinephrine. Analogues **10** and **13** illustrate less favorable substituents for α_1-agonist activity. The *S*-phenyl compound (**10**), while still a reasonably good agonist, is much less potent than its methyl congener **31**, and it is possible that in the case of the phenyl, the degree of bulk which the receptor can efficiently tolerate has been exceeded, although other factors may also account for re-

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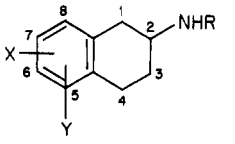
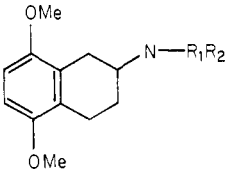
Table II. In Vitro α_1-Agonist Potency of 2-Aminotetralins with Variable Ring Substitution



no.[a]	X	Y	R	EC_{50},[b] M	phentolamine dissoc constant: K_B,[c] nM
18	H	H	H	$>3 \times 10^{-5}$	NA[d]
5	H	5-OMe	H	$2.2 \pm 0.3 \times 10^{-6}$ (10)	7
19	H	8-OMe	H	$1.7 \pm 0.6 \times 10^{-6}$ (6)	12
20	6-OMe	7-OMe	H	$>1 \times 10^{-5}$	NA
21	7-OMe	8-OMe	Et	$>1 \times 10^{-5}$	NA
22	5-OMe	8-OMe	H	$1.2 \pm 0.2 \times 10^{-7}$ (14)	6
2 (methoxamine)				$7.2 \pm 1.0 \times 10^{-7}$ (5)	11

[a] Where optical isomers are possible, compounds are unresolved. [b] See Experimental Section for determination of EC_{50} values. [c] Concentration-response curves before and after phentolamine (10^{-7} M) are determined, and the receptor dissociation constant (K_B) for phentolamine was determined according to the formula: K_B = [phentolamine]/[(EC_{50} in the presence of phentolamine/EC_{50} in the absence of phentolamine) − 1]. A compound is considered to be a postjunctional α_1 agonist if it is blocked by phentolamine with K_B in the range reported for this agent as an α-adrenergic antagonist (5–20 nM). [d] NA = not available. Dissociation constants were not determined for compounds whose EC_{50} values were greater than 10^{-5} M.

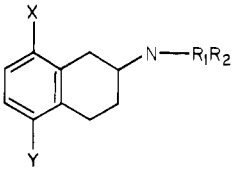
Table III. Effect of Nitrogen Substitution upon α_1-Agonist Potency of 2-Aminotetralins



no.[a]	R_1	R_2	EC_{50},[b] M	K_B,[c] nM
22	H	H	$1.2 \pm 0.2 \times 10^{-7}$ (14)	6
23	H	CH_3	$8.6 \pm 1.1 \times 10^{-8}$ (9)	11
24	CH_3	CH_3	$8.1 \pm 2.5 \times 10^{-8}$ (9)	15
25	H	CH_2CH_3	$8.1 \pm 1.4 \times 10^{-8}$ (5)	8
26	H	$CH_2CH_2CH_3$	$1.1 \pm 0.3 \times 10^{-6}$ (5)	18
2 (methoxamine)			$7.2 \pm 1.0 \times 10^{-7}$ (5)	11

[a-c] See corresponding footnotes to Table II.

Table IV. In Vitro α_1-Agonist Potency of 5,8-Disubstituted 2-Aminotetralins



no.[a]	X	Y	R_1	R_2	EC_{50},[b] M	phentolamine dissoc constant: K_B,[c] nM
7	SCH_3	OCH_3	H	Et	$1.4 \pm 0.3 \times 10^{-7}$ (4)	16
10[d]	OCH_3	SPh	H	Et	7×10^{-7}	NA[e]
12	OCH_3	SCH_3	CH_3	CH_3	$1.4 \pm 0.3 \times 10^{-8}$ (4)	9
13	OCH_3	NH_2	H	Et	$5.3 \pm 0.7 \times 10^{-6}$ (4)	NA
15	Cl	OCH_3	H	H	$2.3 \pm 0.4 \times 10^{-7}$ (5)	13
17	CH_3	CH_3	H	H	1×10^{-5}	NA
22	OCH_3	OCH_3	H	H	$1.2 \pm 0.2 \times 10^{-7}$ (14)	6
27	Cl	OCH_3	H	Et	$6.4 \pm 0.9 \times 10^{-8}$ (6)	14
28	I	OCH_3	H	Et	$6.4 \pm 1.0 \times 10^{-8}$ (6)	12
29	OCH_3	I	H	Et	$2.1 \pm 0.5 \times 10^{-8}$ (9)	11
30	OCH_3	SCH_3	H	H	$1.2 \pm 0.2 \times 10^{-8}$ (4)	5
31	OCH_3	SCH_3	H	Et	$2.6 \pm 0.4 \times 10^{-8}$ (4)	NA
2 (methoxamine)					$7.2 \pm 1.0 \times 10^{-7}$ (5)	11

[a-c] See corresponding footnotes to Table I. [d] Compound is a partial agonist with an intrinsic activity of 0.8 that of norepinephrine. [e] NA = not available.

duced reactivity. The presence of a second basic center in the molecule as in diamine **13** may disorder the agonist binding orientation of this molecule and thus account for its reduced activity relative to **30** or **31**.

Experimental Section

Melting points were determined in open capillary tubes using a Thomas-Hoover Uni-melt apparatus and are uncorrected. Elemental analyses were performed by the Analytical and Physical

Chemistry Section of Smith Kline & French Laboratories. Where analyses are reported by symbols of elements, results were within 0.4% of calculated values. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer. NMR spectra were recorded with a Perkin-Elmer R-24 spectrometer using $(CH_3)_4Si$ or DSS as internal standards. Satisfactory IR, NMR, and mass spectral data were obtained for all new compounds.

Quantitation of Postjunctional α_1-Adrenergic Activity. After sacrifice of a rabbit, a 0.5-cm segment of the central ear artery was dissected free at the base of the ear, cleaned of fat and connective tissue, and mounted in a small (1-mL capacity) chamber, where it is superfused with oxygenated Krebs solution. The segment was suspended between two tungsten wires, one attached to the chamber and the other to a force-displacement transducer so that circular smooth muscle tension could be measured directly. Before administration of the test drug, norepinephrine (NE) was administered in increasing concentration (10^{-8} to 3×10^{-6} M) to determine the maximum response of the artery. Each concentration was allowed to remain in contact with the tissue until a stable response was attained, at which time the next higher concentration was administered to produce a cumulative concentration–response curve. The EC_{50} is that concentration of compound which produces 50% of the maximum response to norepinephrine. After the NE was washed out, a cumulative concentration–response curve for the test drug was determined. If the effect of α blockade was to be determined, phentolamine superfusion was begun after washout of the test drug. Following a 30-min equilibration period, concentration–response curves for NE and the test drug were determined in the presence of phentolamine. Throughout the test procedure, 2×10^{-6} g/mL of cocaine was used to block neuronal uptake and rule out indirect effects due to catecholamine release from presynaptic nerve terminals. Confirmation of the direct nature of the induced vasoconstriction was obtained by doing the assay with a tissue segment from a rabbit which had been pretreated for 18 h with 5 mg/kg of reserpine iv to deplete stores of endogenous transmitters.[22] The EC_{50} values for all compounds reported in the tables were not changed by this reserpine pretreatment. Vasoconstriction due to the presence of postjunctional α_2 receptors has been ruled out by the characterization of the rabbit ear artery as a tissue in which α_2 receptors are not present as evidenced by the ability of prazosin to completely block the constrictor response to exogenously administered NE, while yohimbine is ineffective at blocking this response.

5-Methoxy-2-aminotetralin Hydrochloride (5). A solution of 5-methoxy-2-tetralone (35 g, 0.2 mmol) and methoxyamine hydrochloride (25 g, 0.3 mol) in 10 mL of ethanol containing the minimum amount of H_2O necessary to effect solution was titrated with 1 N NaOH to pH 8.2. The solution was concentrated, diluted with H_2O, and extracted with Et_2O, and the extracts were dried over $MgSO_4$ and concentrated to give 35 g of a colorless oil. This was dissolved in 50 mL of THF and treated with 50 mL of 1 M borane in THF, and the solution was refluxed for 3 h. Concentrated hydrochloric acid (25 mL) was added, and the mixture was refluxed for 15 min. The resulting precipitate was removed by filtration to give 63% of a white solid, mp 260–264 °C dec.

***N*-(1,2,3,4-Tetrahydro-8-iodo-5-methoxy-2-naphthalenyl)acetamide (6).** The amine **5** was acylated with 1.5 equiv of acetyl chloride in CH_2Cl_2/2.5 N NaOH. Iodination of this amide according to the procedure used for the synthesis of **9** gave the product in 78% yield as white crystals, mp 212–214 °C.

1,2,3,4-Tetrahydro-5-methoxy-*N*-ethyl-8-(methylthio)-2-naphthalenamine Hydrochloride (7). The iodide was displaced according to the procedure for the preparation of **11**. Reduction with diborane gave **7** as a white solid in 68% overall yield, mp 208–209 °C.

***N*-(1,2,3,4-Tetrahydro-5-iodo-8-methoxy-2-naphthalenyl)acetamide (9).** To a suspension of 2.19 g (0.01 mol) of **8** and 2.21 g (0.01 mol) of silver trifluoroacetate in 80 mL of CH_2Cl_2 was added dropwise a solution of iodine (2.52 g, 0.02 mol) in 80 mL of CH_2Cl_2. The reaction mixture was stirred for 1 h at 25 °C, filtered, and evaporated to leave an oil to which 100 mL of H_2O was added. After 30 min the oil solidified, and the crystals were collected, dried, and recrystallized from EtOH to give 2.50 g (72%) of acetamide **9** as a white solid, mp 202–203 °C.

***N*-[1,2,3,4-Tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenyl]acetamide (11).** To a solution of 2.25 g (0.042 mol) of methylthiolithium in 22.5 mL of DMF was added 2.4 g (0.007 mol) of **9** and 1.35 g (0.094 mol) of Cu_2O. The mixture was heated to 80 °C for 3 h under argon. The reaction was cooled, diluted with 150 mL of $CHCl_3$, and filtered through Celite. The filtrate was washed with H_2O, dried, and evaporated to give 1.8 g of **11** (98%) as a white solid, mp 190 °C.

1,2,3,4-Tetrahydro-8-methoxy-*N*-methyl-5-(phenylthio)-2-naphthalenamine Hydrochloride (10). To a solution of 2.0 g (5.8 mmol) of **9** in 20 mL of dry THF at −78 °C was added 1.45 g (23.2 mmol) of *n*-butyllithium. The solution was stirred for 30 min and then treated with 2.52 g (116 mmol) of diphenyl disulfide in 5 mL of THF. It was stirred at 25 °C for 16 h, decomposed with 25 mL of H_2O, concentrated, and extracted with Et_2O. The Et_2O extracts were dried and evaporated to an oil, which was chromatographed on silica gel and eluted with 1:1 Et_2O–EtOAc. Recrystallization from MeOH–Et_2O gave 900 mg (47%) of *N*-[1,2,3,4-tetrahydro-8-methoxy-5-(phenylthio)-2-naphthalenyl]-acetamide as a white solid, mp 145–154 °C. To a solution of 500 mg of this in 25 mL of dry THF was added 10 mL of a 1 M solution of borane in THF. The reaction mixture was refluxed for 2 h, cooled, treated with 20 mL of 3 N hydrochloric acid, and refluxed for 20 min. It was concentrated and diluted with ice–water (50 mL). The resulting crystals were filtered and dried. Crystallization from MeOH–EtOAc gave 270 mg (54%) of white solid, mp 226–228 °C.

1,2,3,4-Tetrahydro-8-methoxy-*N*,*N*-dimethyl-5-(methylthio)-2-naphthalenamine Hydrochloride (12). A solution of 1.1 g (5 mmol) of **30** in 1.5 mL of 98% formic acid and 1.7 mL of 37% formaldehyde was heated at 100 °C for 6 h and then stirred for 16 h at 25 °C. The mixture was acidified with 10 mL of 3 N hydrochloric acid, washed with Et_2O, and made alkaline with ammonium hydroxide. It was extracted with CH_2Cl_2, dried over $MgSO_4$, and concentrated to an oil. This was chromatographed on silica gel, eluting with 95:5 CH_2Cl_2–MeOH. The product was dissolved in Et_2O and treated with ethereal HCl. The resulting precipitate was collected, washed with Et_2O, and dried to give 0.36 g (25%) of **12** as a white solid mp 215–217 °C.

1,2,3,4-Tetrahydro-*N*^{2}-ethyl-8-methoxy-2,5-naphthalenediamine Dihydrochloride (13). A solution of 219 mg (1 mmol) of **8** in 7.5 mL of trifluoroacetic acid was treated with 140 mg of sodium nitrate in one portion. It was stirred for 1 h at 25 °C, poured into excess 5% sodium bicarbonate solution, and extracted well with CH_2Cl_2. The combined extracts were washed with H_2O, dried, and evaporated to give crystals. Recrystallization from EtOAc gave 215 mg (80%) of acetamide as white crystals, mp 205–206 °C. A solution of 180 mg of this in 30 mL of EtOH was hydrogenated for 30 min at 50 psi over 30 mg of PtO_2. The reaction was filtered through Celite and treated with ethereal hydrogen chloride. The resulting precipitate was collected and crystallized from EtOH–EtOAc to give white crystals, mp >260 °C dec. This was suspended in 10 mL of THF, 10 mL of 1 M BH_3 in THF was added, and the mixture was refluxed for 7 h. The solution was treated with 15 mL of concentrated HCl, refluxed for 1 h, and cooled in ice, and the resulting precipitate was removed and crystallized from MeOH to give 135 mg (87%) of white crystals, mp >202 °C dec.

1,2,3,4-Tetrahydro-8-chloro-5-methoxy-2-naphthalenamine Hydrochloride (15). A solution of 2.7 g (10 mmol) of ester **14** in 60 mL of EtOH was hydrogenated at 50 psi for 5 h over 60 mg of PtO_2. The mixture was filtered, and the filtrate was treated with 2.5 N NaOH (10 mL) and refluxed for 3 h. It was worked up to give 1.9 g of tan crystals. Crystallization from toluene gave 1.4 g (58%) of beige crystals, mp 183–186 °C. A suspension of 2.4 g (10 mmol) of this acid (combined from two runs) in 50 mL of $SOCl_2$ was refluxed for 2 h. Excess $SOCl_2$ was stripped off, and the residual acid chloride was taken up in 50 mL of acetone and treated with 1.3 g (20 mmol) of NaN_3 in a minimum amount of H_2O. After stirring for 20 min, 50 mL of H_2O was added, and the resulting precipitate was removed by filtration and dried. It

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was suspended in 50 mL of toluene, heated to reflux for 1 h, treated with 3 mL of concentrated HCl, and refluxed for an additional hour. It was cooled and filtered. Recrystallization from EtOH–Et_2O gave 1.6 g (63%) of white needles, mp 235–237 °C dec.

1,2,3,4-Tetrahydro-5,8-dimethyl-2-naphthalenamine Hydrochloride (17). A solution of 4.0 g (24.3 mmol) of 2,5-dimethylphenylacetic acid and 3.6 g (30 mmol) of $SOCl_2$ was stirred at 25 °C for 16 h. Excess $SOCl_2$ was removed, and the residue was dissolved in 30 mL of CH_2Cl_2. This was added to a suspension of 33 g (25 mmol) of $AlCl_3$ in 60 mL of CH_2Cl_2 in a dry-ice bath. Ethylene was bubbled through the mixture vigorously for 7 min, and the reaction was allowed to warm to 25 °C and stirred for 30 min. The reaction was quenched with H_2O, and the layers were separated, washed with 3 N HCl and 5% $NaHCO_3$, dried, and evaporated. The residue was quickly chromatographed over silica gel eluting with 70:30 cyclohexane–Et_2O to give 2.0 g (47%) of tan oil. This was dissolved in 50 mL of dry MeOH containing 8.0 g of NH_4OAc. Sodium cyanoborohydride (3.3 g, 55 mmol) was added, and the mixture was stirred for 16 h. The reaction was treated carefully with 15 mL of concentrated HCl and stirred for 1 h. The MeOH was removed, and the residue was partitioned between Et_2O and H_2O. The aqueous layer was separated, made basic, and extracted again with Et_2O. The basic extracts were dried and treated with HCl/Et_2O. The resulting precipitate was removed by filtration and crystallized from MeOH–EtOAc to give 0.40 g (22%) of white solid, mp 243–245 °C.

1,2,3,4-Tetrahydro-8-chloro-*N*-ethyl-5-methoxy-2-naphthalenamine Hydrochloride (27). The primary amine **15** was acylated with acetyl chloride and reduced with diborane to give **27** as white crystals, mp 255–257 °C dec.

Preparation of Aminotetralins 20, 25, 26, 28, 29 and 31. Compound **20** was obtained by acetylation and diborane reduction of 6,7-dimethoxy-2-aminotetralin.[24] Compounds **25** and **26** were prepared by acylation of **22** with acetyl or propionyl chloride, followed by diborane reduction. Compounds **28**, **29**, and **31** were synthesized by diborane reduction of the corresponding acetamides **6**, **9**, and 11.

1,2,3,4-Tetrahydro-8-methoxy-5-(methylthio)-2-naphthalenamine Hydrochloride (30). A solution of 1.0 g (3.8 mmol) of 11 in 100 mL of toluene containing 0.474 g (6 mmol) of pyridine was heated to 65 °C. Phosphorus pentachloride (1.25 g, 6 mmol) was added and heating continued for 2 h. The toluene was removed under reduced pressure, 200 mL of MeOH was added, and the solution was stirred overnight at 25 °C. The MeOH was evaporated and 100 mL of 1:1 THF–H_2O was added. After 30 min the THF was removed and the aqueous layer was extracted with Et_2O. It was made alkaline with NH_4OH and extracted with 3 portions of CH_2Cl_2. The combined extracts were dried and evaporated to yield free base as an oil. This was dissolved in Et_2O and treated with excess ethereal HCl. The resulting precipitate was removed by filtration and recrystallized from MeOH–EtOAc–Et_2O to give 0.45 g (45%) of a white solid, mp 290 °C dec.

7,8-Dimethoxy-2-aminotetralin (21). The compound was prepared by the method of Barfknecht et al.,[24] starting with 2,3-dimethoxybenzyl chloride. It was recrystallized from 2-propanol–ether as colorless rosettes, mp 212–213 °C.

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Mammary Tumor Inhibiting Effect of 3,3′-Diacetoxy-α,β-dialkylstilbenes and of Related Stilbene Oxides

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3,3′-Diacetoxy-α,β-dialkylstilbenes (alkyl = CH_3 to C_4H_9, **1–4**), 3,3′-dihydroxy-α,β-diethylstilbene (**5**), and their corresponding stilbene oxides (**6–10**) were synthesized. Compounds **1–10** competitively antagonized in vitro the interaction of [^{3}H]estradiol with its receptor. 3,3′-Diacetoxy-α,β-diethylstilbene (**2**), 3,3′-diacetoxy-α,β-diethylstilbene oxide (**7**), and their phenolic analogues (**5** and **10**) were most effective. Shortening or lengthening the alkyl side chains led to a decrease in receptor affinity. Among the stilbenes and epoxides, those with C_2H_5 and C_3H_7 groups (**2**, **3**, **5** and **7**, **8**, **10**) caused the strongest inhibition of the growth of a hormone-dependent postmenopausal human mammary carcinoma serially implanted in nude mice. The strong antitumor activity of **5** and **10** was confirmed by experiments on the 9,10-dimethyl-1,2-benzanthracene-induced, hormone-dependent mammary carcinoma of the Sprague–Dawley rat.

The displacement of the phenolic hydroxy groups of the synthetic estrogens 4,4′-dihydroxy-α,β-dialkylstilbenes into the 3,3′ positions led to compounds with antiestrogenic and mammary tumor inhibiting properties.[1,2] Since the transformation of 4,4′-dihydroxy-α,β-diethylstilbene into its oxide did not cause a reduction of the affinity to the estradiol receptor and since this oxide exhibits a strong mammary tumor inhibiting effect,[3] these 3,3′-dihydroxy-α,β-dialkylstilbenes were connected with the potentially alkylating epoxide group. Thus, it might be possible to get compounds with antiestrogenic and cytotoxic properties that might have a more selective effect on the hormone-dependent mammary carcinoma because of their affinity to the estradiol receptor than common cytostatic drugs.

Chemistry. 3,3′-Diacetoxy-α,β-dialkylstilbenes **1–4** were prepared from the corresponding 3,3′-dihydroxy com-

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