clear, viscous liquid: yield 59%; MS, m/e (relative intensity) 203 (M^+, 22), 187 (72). This material was used without further purification.

1-(1-Phenylcyclooctyl)piperidine (8) was made by refluxing 11 with 1,5-dibromopentane and K_2CO_3 in DMF: yield 19% (0.69 g); mp 183–185 °C; IR (KBr) 3420, 2940, 3500–3670, 1450, 1205, 1030, 950, 870, 760, 700 cm^{-1}; MS, m/e (relative intensity) 272 (68), 271 (M^+, 100). Anal. ($C_{19}H_{30}ClN$), C, H, N.

[^{3}H]PCP Binding Assay. The binding assay was performed as described by Zukin and Zukin.[17] Aliquots of freshly prepared rat brain homogenate (1.0 mL) were incubated at 4 °C for 45 min with 7.0 nM [^{3}H]PCP, and the binding of [^{3}H]PCP to the membrane preparation was measured by filtration assay. The glass-fiber filter was pretreated with water saturated with *tert*-amyl alcohol to reduce binding to the filter. This treatment eliminated approximately 90% of [^{3}H]PCP binding to the glass-fiber filter. The nonspecific binding in the presence of 0.1 mM PCP was subtracted from the total binding to yield specific binding. A concentration–displacement curve for each analogue was visually fitted from a log-probit plot, and the IC_{50} of each analogue was compared to that of PCP, which was used as a standard in each assay.

Discriminative Stimulus Assay. Male, Fischer-derived CDF rats were trained to discriminate between PCP and saline in a two-choice, discrete-trial avoidance task similar to that described in detail elsewhere.[4] PCP (3.0 mg/kg) or saline was administered intraperitoneally 30 min prior to a training session. Each experimental session consisted of 20 trials, and the rats were trained until they reliably completed at least 90% of the 20 trials on the appropriate choice lever. When acquisition of the discrimination was completed, drug testing sessions were interposed among training sessions. During training sessions, only a response on the appropriate choice lever terminated a trial; during test sessions, a response on either choice lever terminated a trial. A dose of a test drug was considered to produce stimuli which generalized to those produced by PCP if the group of rats completed a mean of at least 90% of the 20 trials on the PCP-appropriate choice lever. Relative potencies were determined by using standard bioassay statistics. PCP produced dose-related discriminative stimuli when tested over a greater than tenfold dose range.

Acknowledgment. The authors thank Mr. W. G. Marquardt and Ms. W. M. Roberts for their aid in the preparation of this manuscript.

α-Adrenergic Agents. 1. Direct-Acting α_1 Agonists Related to Methoxamine[1]

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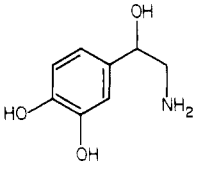
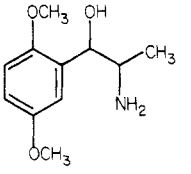
A series of phenylethylamines related to methoxamine has been prepared and evaluated for direct α_1-receptor agonist activity. It has been observed that for open-chain compounds such as methoxamine, in which the amine-containing portion is free to adopt numerous conformations, an hydroxyl group is necessary for direct α_1-adrenergic activity. When the hydroxyl is removed, however, the direct component of activity is greatly reduced unless the amine is incorporated into a more sterically defined structure. From our studies we have concluded that in order for a phenylethylamine to be active as a direct α_1-receptor agonist it should have a β nitrogen in a fully extended conformation relative to a substituted phenyl ring. For optimum potency, the nitrogen should be exocyclic to a saturated six-membered ring. It may be further incorporated exocyclic or endocyclic into an additional ring so long as the amine occupies a well-defined region of space relative to the aromatic portion of a molecule. The ED_{50} values of some of the more potent compounds as α_1-receptor agonists are on the order of 1×10^{-7} M.

The phenylethylamines are a well-studied class of pharmacological agents which over the years have been the subject of numerous investigations. In the last decade there have been many studies into the α-adrenergic effects of a variety of phenylethylamines with rigid, as well as flexible, structures[2-8] (and references therein). At the same time, much evidence has been accumulating which indicates that α receptors can be subdivided into at least two pharmacologically distinct classes which can be functionally differentiated by their ability to interact with a series of agonists and antagonists.[9,10] In addition to the classical postsynaptic α adrenoceptor (α_1) that mediates the responses of effector organs to norepinephrine, there are also α receptors (α_2) on noradrenergic nerve terminals which modulate the release of norepinephrine in the periphery and the central nervous system.[11-13] This subclassification of α adrenoceptors opens new possibilities for drug discovery through the development of agonists or antagonists having a high degree of selectivity for each receptor subtype.

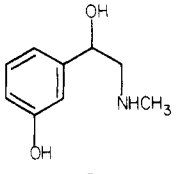
Norepinephrine (1), the endogenous transmitter of the



1



2



3

sympathetic nervous system, acts with almost equal potency on both α_1 and α_2 receptors.[9] Other agents, such as methoxamine (2) or phenylephrine (3), are much more specific for the α_1 than for the α_2 receptor and represent attractive points of departure for the development of se-

(1) This paper has been presented in part. See "Abstracts of Papers", 181st National Meeting of the American Chemical Society, New York, Aug, 1981, American Chemical Society, Washington, DC, 1981, Abstr MEDI 12.
(2) P. Burn, P. A. Crooks, B. L. Ratcliff, and J. M. H. Rees, *J. Pharm. Pharmacol.*, **32**, 87 (1980).
(3) G. L. Gruenwald, G. L. Ruth, J. A. Kroboth, T. R. Kamdar, B. V. Patil, and K. N. Salman, *J. Pharm. Sci.*, **65**, 920 (1980).
(4) H. C. Chang, J. P. Long, D. E. Nichols, and C. F. Barfknecht, *J. Pharmacol. Exp. Ther.*, **188**, 114 (1974).
(5) D. B. Rusterholz, J. P. Long, J. R. Flynn, and J. R. Glyn, *Arch. Int. Pharmacodyn. Ther.*, **232**, 246 (1978).
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(8) D. B. Rusterholz, S. E. Dryer, J. P. Long, C. F. Barfknecht, and J. Mott, *Eur. J. Pharmacol.*, **65**, 201 (1980).
(9) S. Berthelsen and W. A. Pettinger, *Life Sci.*, **21**, 595 (1977).
(10) C. Melchiorre, *Farmaco, Ed. Sci.*, **35**, 535 (1980).
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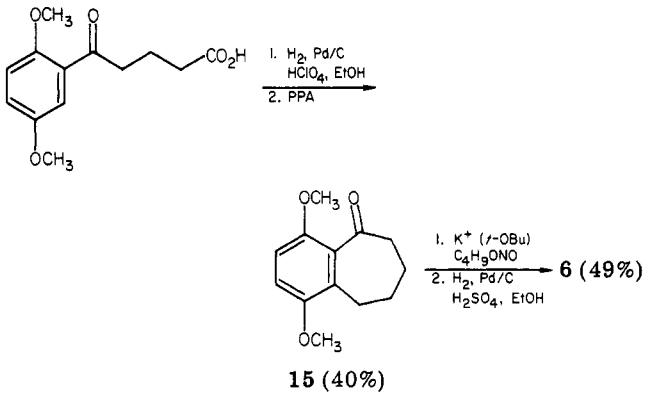
Scheme I



lective α_1-adrenergic agonists.

Investigations into the pharmacological properties of α-adrenergic agents of the phenylethanolamine structures related to norepinephrine have been carried out in a fair amount of detail,[14-16] but far less work has been done on the systematic investigation of direct-acting phenylethylamines as α_1 agonists.

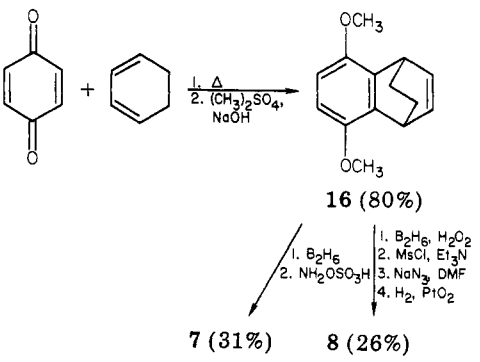
In this paper we report the synthesis and direct peripheral α_1-adrenergic activity of a series of phenylethylamines related to methoxamine. These have been prepared and evaluated in vitro in order to determine the structural requirements for α_1 agonism. The effects of ring size, substitution, and side-chain orientation upon activity were measured and shown to present a self-consistent picture of the requirements for α_1-receptor stimulation.

Chemistry. The 2-amino-4,7-dimethoxyindan (**4**) was prepared by the method of Coutts.[17] Compound **14** was obtained from 2-tetralone by known procedures.[7] The six-membered 5,8-dimethoxy-2-aminotetralin[15] (**5**) was synthesized from 5,8-dimethoxy-2-tetralone[18] by reductive amination with sodium cyanoborohydride. The corresponding seven-membered analogue, 1,4-dimethoxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene (**6**), was prepared as shown in Scheme I by cyclization of 5-(2,5-dimethoxyphenyl)-5-oxopentanoic acid to the cyclic ketone **15**, followed by oximation and reduction.

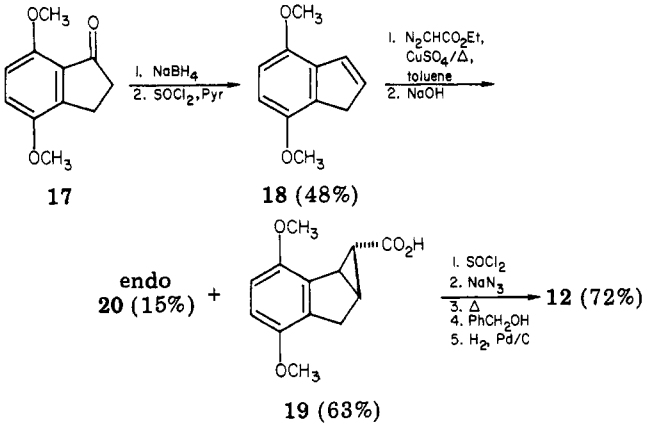
Both the *exo*- and *endo*-ethanonaphthalenes were prepared from the symmetrical bicyclic olefin **16**.[19] Hydroboration of **16**, followed by direct amination with hydroxylamine-*O*-sulfonic acid gave the exo amine **7**. Oxidation of the intermediate organoborane with hydrogen peroxide yielded the alcohol of similar stereochemistry to **7**. Formation of the mesylate and SN_2 displacement with sodium azide gave an azide of opposite stereochemistry, which was catalytically reduced to the endo amine **8** (Scheme II).

The tricyclic cyclopropylamine **12** could be synthesized from ketone **17**.[17] Addition of ethyl diazoacetate to olefin **18** gave a mixture of endo and exo esters, which were separated by chromatography on silica gel. Stereochemical assignments were made by ^1H NMR on the ethyl esters.

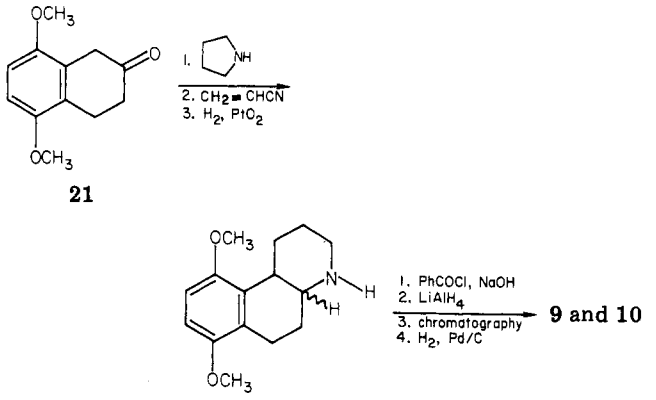
Scheme II



Scheme III



Scheme IV



The ethyl group of the ester of endo isomer **20** is located above the plane of the aromatic ring and, hence, the methylene proton absorptions are shifted upfield (δ 3.5) relative to those of the ester of exo isomer **19** (δ 4.3). Curtius rearrangement on the exo acid **19** proceeded with retention of stereochemistry to give **12** (Scheme III).

The syntheses of both *cis*- and *trans*-octahydrobenzoquinolines **9** and **10** were undertaken from 2-tetralone **21**.[18] Cyanoethylation of the pyrrolidine enamine of **21**, followed by reductive cyclization of the nitrile, gave a mixture of cis and trans isomers, which could not be conveniently separated. Benzoylation, followed by lithium aluminum hydride reduction, gave the benzyl derivatives, which were efficiently separated by chromatography on silica gel to give pure samples of both *cis*- and *trans*-benzylamines. Assignment of stereochemistry was done by analysis of the vicinal coupling constants of the benzylic hydrogens. The benzylic protons of the trans isomer appeared as an AB quartet (δ 3.78) with a chemical-shift difference of 66 Hz

(14) A. Burger, Ed. "Drugs Affecting The Peripheral Nervous System", Marcel Dekker, New York, 1967, and references therein.
(15) L. S. Goodman and A. Gilman, Ed. "The Pharmacological Basis of Therapeutics", MacMillan, New York, 1975.
(16) G. Leclerc, J. C. Bizec, N. Bieth, and J. Schwartz, *J. Med. Chem.*, **23**, 738 (1980).
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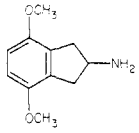
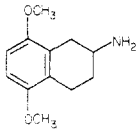
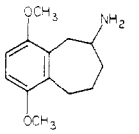
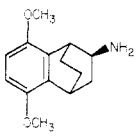
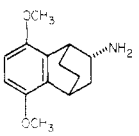
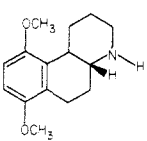
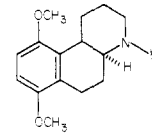
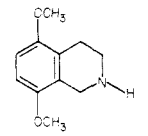
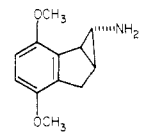
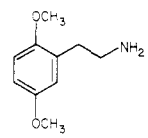
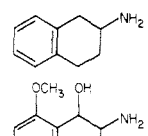
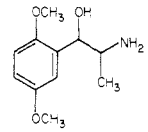
(19) O. Diels and K. Adler, *Ber. Dtsch. Chem. Ges.*, **62**, 2081 (1929).

Table I. In Vitro α_1-Adrenergic Agonist Activity

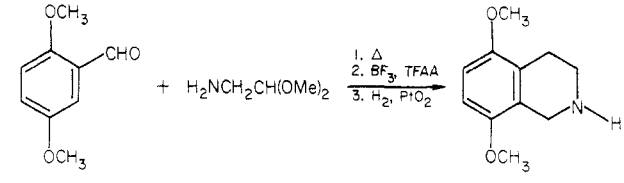
no.	structure[a]	EC_{50},[b] M	phentolamine dissoc constant (K_B),[c,d] nM
4		$>3 \times 10^{-5}$	NA[e]
5		$1.2 \pm 0.2 \times 10^{-7}$ (14)	6
6		$5.3 \pm 1.1 \times 10^{-6}$ (5)	11
7		3×10^{-5}	NA
8		3×10^{-5}	NA
9		$1.7 \pm 0.3 \times 10^{-7}$ (7)	11 ± 0.6 (3)
10		$2.0 \pm 0.4 \times 10^{-7}$ (7)	14.7 ± 3.9 (4)
11		$>3 \times 10^{-5}$	NA
12		$3.4 \pm 0.7 \times 10^{-7}$ (9)	8.4 ± 1.6 (4)
13		$1.1 \pm 0.1 \times 10^{-5}$ (5)	54 ± 15 (5)[f]
14		$>3 \times 10^{-5}$	NA
2[g]		$7.2 \pm 1.0 \times 10^{-7}$ (4)	9.8 ± 1.8 (4)

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

(J = 13 Hz), while those of the cis isomer appeared as a broadened singlet (δ 3.8). These values correlate well with those of previously reported stereochemical studies.[20,21] Removal of the benzyl protecting group from both cis and trans isomers was carried out by hydrogenolysis over a palladium catalyst (Scheme IV).

Tetrahydroisoquinoline **11** was synthesized from 2,5-dimethoxybenzaldehyde by condensation with aminoacetaldehyde dimethyl acetal, followed by ring closure and hydrogenation of the resulting isoquinoline (Scheme V).

Scheme V



11 (43%)

Results and Discussion

Norepinephrine is about equipotent as an agonist at both α_1 and α_2 receptors, while both methoxamine (**2**) and phenylephrine (**3**) are selective for the α_1 receptor.[9] Potency at the α_1 receptor is determined by the ability of a compound to induce vasoconstriction in the isolated rabbit ear artery. The constriction must be clearly blocked by phentolamine and not reduced by pretreatment of the preparation with reserpine. Thus, constriction under these conditions is mediated by direct-acting postjunctional α_1 agonists (see Experimental Section).

When the benzylic hydroxyl of methoxamine is removed, the phenylethylamine obtained, **13** is about 20-fold weaker than methoxamine (Table I). While **13** is certainly free to assume any conformation that is available to methoxamine, the removal of the hydroxyl group may take away a hydrogen-bonding interaction that favors population of a conformational state of the molecule which can interact effectively with the receptor. If the hydroxyl is intramo-

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(21) R. E. Lyle and L. N. Pridgen, *J. Org. Chem.*, **38**, 1618 (1973).
(22) J. P. Long, D. B. Rusterholz, J. R. Flynn, and J. G. Cannon, *Adv. Biosci.*, **20**, 281, 1980.
(23) W. A. Noyes, in "Organic Syntheses", Collect. Vol. 2, Wiley, New York, 1943, p 108.
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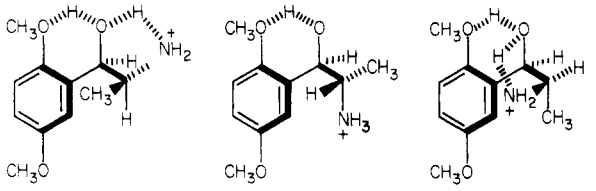
(25) C. F. Barfknecht, D. E. Nichols, D. B. Rusterholz, J. P. Long, J. A. Englebrecht, J. M. Beaton, R. J. Bradley, and D. C. Dyer, *J. Med. Chem.*, **16**, 804 (1973).

Chart I[a]



A B C

[a] Erythro isomer.

lecularly hydrogen bonded with the adjacent methoxyl through a six-membered ring, the possible orientation of the side chain are limited. The three most likely conformations of methoxamine are then reduced to A, B, and C in Chart I. At physiological pH (~7.4), a significant amount of the nitrogen would be protonated, and hydrogen bonding of the hydroxyl to this adjacent nitrogen should influence the molecular conformation and would favor conformations A and C over B, in which bonding to nitrogen is precluded. The ^1H NMR of methoxamine shows an H–H coupling constant of 4.5 Hz. This is indicative of a dihedral angle of ~60°, which would be in agreement with conformers A and C but not B. All three conformations can be mimicked by compounds **5**, **8**, and **11** (Table I). These compounds were synthesized and tested for α_1-receptor agonist activity using the isolated perfused rabbit ear artery (see Experimental Section).

The data in Table I substantiate the hypothesis that the benzylic alcohol of methoxamine is not necessary for direct adrenergic activity but may direct the amine into an orientation in which it can interact directly with the receptor. Of the three compounds which were prepared to mimic the conformations of methoxamine, two (**11** and **8**) were essentially inactive and one (**5**) was very potent. Tetrahydroisoquinoline **11** has a folded conformation, while in the bicyclooctane **8** the conformation of the amine is synclinical (60°) relative to the aromatic ring. Both are very weak ($ED_{50} > 3 \times 10^{-5}$ M) as α_1 agonists. The low activity of **11** is not unexpected, since the conformation of methoxamine represented by **11** is unfavored. It is possible that for compound **8** the introduction of the two-carbon bridge provides a very unfavorable steric interaction which could account for the low potency of this molecule. On the other hand, 2-aminotetralin **5** seems more potent than methoxamine and demonstrates that appropriate orientation of the amine relative to the aromatic ring is in this case sufficient to induce direct α_1-agonist activity. Furthermore, very small changes in structure as seen by the addition or elimination of a single methylene (compounds **4** and **6**) are sufficient to decrease the potency over 100-fold. Similarly, loss of the aromatic methoxyl groups (compound **14**) causes a great decrease in potency by eliminating what is apparently an important recognition site in the aromatic ring which orients the molecule at the receptor site.

The idea that a β-phenethylamine in a fully extended conformation relative to an appropriately substituted phenyl ring is an important structural component necessary for selective α_1-agonist activity is further supported by data from two other series of compounds. The *exo*-cyclopropylamine **12** and the octahydrobenzoquinolines **9** and **10** contain an amine exocyclic to a substituted six-membered ring in an extended conformation and all are potent as agonists ($ED_{50} \approx 2 \times 10^{-7}$ M).

In summary, these results suggest that methoxamine most probably interacts with the postjunctional α_1 receptor in a fully extended conformation. The benzylic hydroxyl is not necessary for activity but may direct the amine into a favorable orientation for receptor interaction. This is supported by the observations that phenylethylamines with unrestricted conformations, such as **13**, are less potent as direct α_1 agonists than those with well-defined orientations, such as **5**. There are also important recognition sites on the aromatic ring which are necessary for agonist potency. Substitution of methoxy at these sites (positions **5** and **8**) gives compounds of high potency.

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 Me_4Si or DSS as internal standard. Satisfactory IR and NMR spectral data were obtained for all reported compounds. Compound **13** was supplied by Professor Castignoli from the University of California at San Francisco.

Determination 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 concentrations (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 NE. After washout of the NE, 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 equilibrium 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, thus, 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 same 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 transmitter.[26] The EC_{50} values for all compounds reported in Table I were not changed by this reserpine pretreatment. Vasoconstriction due to the presence of postjunctional α_2 receptors has been ruled out by characterization of the rabbit ear artery as a tissue in which α_2 receptors were 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.

1,4-Dimethoxy-6-amino-6,7,8,9-tetrahydro-5*H*-benzocycloheptene Hydrochloride (6). To a suspension of 10.1 g of potassium *tert*-butoxide (0.09 mol) in 150 mL of EtOH and 150 mL of Et_2O was added dropwise a solution of 9.9 g (0.045 mol) of ketone **15** and 9.3 g (0.09 mol) of freshly prepared *n*-butyl nitrite[23] in 100 mL of Et_2O. The mixture was stirred in an ice bath for 2 h and then at 25 °C overnight. It was diluted with 300 mL of H_2O and extracted with Et_2O. The aqueous phase was acidified to pH 1.0 and extracted with three portions of Et_2O. The combined extracts were dried and evaporated to give 6.2 g (55%) of oxime as a yellow solid. A solution of 1.99 g of this oxime in 50 mL of glacial acetic acid containing 1 g of sulfuric acid was

(26) P. A. Shore, J. S. Olin, and B. B. Brody, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **16**, 335 (1957).

hydrogenated over 1 g of 10% Pd/C at 40 psi for 4 h. The mixture was filtered through Celite, and the catalyst was washed 4 × 50 mL of H_2O. The filtrate was neutralized to pH 10.0 with sodium hydroxide and extracted with three portions of Et_2O. The combined extracts were washed with H_2O, dried, and treated with 10 mL of HCl/Et_2O. The resulting precipitate was collected and dried to give 1.42 g (89%) of white solid, mp 233–238 °C. Anal. ($C_{13}H_{19}NO_2$·HCl) C, H, N.

2-*exo*-Amino-5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-ethanonaphthalene Hydrochloride (7). To a solution of 780 mg (206 mmol) of sodium borohydride in 50 mL of diglyme was added 10.8 g (50 mmol) of olefin **16**. The mixture was cooled in an ice bath while 3.90 g (27.5 mmol) of BF_3·Et_2O was added dropwise. It was stirred at 25 °C for 12 h and then treated with 6.22 g (55 mmol) of hydroxylamine-*O*-sulfonic acid in 25 mL of diglyme. The solution was heated to 100 °C for 3 h, cooled, and treated with 20 mL of concentrated HCl. It was poured into 200 mL of H_2O and extracted with Et_2O, which was discarded. The aqueous phase was adjusted to pH 11.0 with 40% aqueous NaOH, and the mixture was extracted well with Et_2O. The combined extracts were washed, dried, and evaporated to leave a yellow oil. This was dissolved in 100 mL of Et_2O and treated with excess ethereal HCl. The resulting precipitate was collected, washed, and dried to give 4.1 g (31%) of white solid, mp 241–247 °C.

2-*endo*-Amino-5,8-dimethoxy-1,2,3,4-tetrahydro-1,4-ethanonaphthalene Hydrochloride (8). To a stirred suspension of 0.76 g (0.02 mol) of sodium borohydride and 4.32 g (0.02 mol) of olefin **16** in 50 mL of dry THF was added 3.69 g (0.026 mol) of BF_3·Et_2O. The reaction mixture was stirred at 25 °C for 16 h and hydrolyzed by the *cautious* addition of 10 mL of H_2O. After bubbling had ceased, 10 mL of 10% aqueous NaOH was added, followed by 10 mL of 30% H_2O_2. After the mixture was stirred for 1 h, th THF was removed and an additional 100 mL of H_2O was added. The aqueous portion was extracted with three 50-mL portions of CH_2Cl_2, and the extracts were dried, filtered, and evaporated to give 4.6 g (100%) of alcohol as a viscous oil. A solution of 3.74 g (0.016 mol) of this alcohol in 80 mL of dry CH_2Cl_2 was treated with 2.42 g of Et_3N (0.024 mol), followed by 2.06 g (0.018 mol) of mesyl chloride. The reaction was stirred for 30 min and then washed with H_2O, 3 N HCl, and saturated $NaHCO_3$. The organic layer was dried and evaporated to give the mesylate which, without further purification, was dissolved in 25 mL of dry DMF and treated with 2.08 g (0.032 mol) of sodium azide. The mixture was heated to 80 °C for 5 days, diluted with 150 mL of H_2O, and extracted with 3 × 50 mL of CH_2Cl_2. The extracts were washed, dried, and evaporated to give a brown oil. Chromatography over silica gel eluting with CH_2Cl_2 gave 2.28 g of azide (55%) as a colorless oil. A solution of 1.81 g of this azide in 100 mL of EtOH was hydrogenated at 50 psi over 0.1 g of PtO_2 for 7 h. The reaction was filtered through Celite, and the filtrate was evaporated. The residual oil was dissolved in 100 mL of Et_2O and treated with excess HCl/Et_2O. The resulting precipitate was collected, washed with Et_2O, and dried to give 0.89 g (47%) of pale yellow crystals, mp 99–105 °C (26% overall from olefin). Anal. ($C_{14}H_{19}NO_2$·HCl) C, H, N.

1,1a,6,6a-Tetrahydro-2,5-dimethoxycycloprop[*a*]inden-1-amine Hydrochloride (12). Into 10 mL of CH_2Cl_2 was dissolved 468 mg (2 mmol) of acid **19**. The solution was treated with 2 mL of $SOCl_2$ and evaporated, and the residue was taken up in CH_2Cl_2 and evaporated again to leave a yellow oil. This was dissolved in 5 mL of acetone, treated at 25 °C with 260 mg (4 mmol) of sodium azide in 1 mL of H_2O, and extracted with three 40-mL portions of CH_2Cl_2. The extracts were dried and evaporated to give 510 mg of acyl azide as an off-white solid. This was dissolved in 12 mL of toluene and refluxed for 30 min. A solution of 216 mg of benzyl alcohol in 5 mL of toluene was added, and the mixture was refluxed overnight. The toluene was evaporated and the residue was recrystallized from MeOH to give 505 mg of benzyl carbamate. This was dissolved in 25 mL of EtOH, treated with 100 mg of 10% Pd/C and 4 drops of concentrated HCl, and hydrogenated at 50 psi for 45 min. The mixture was filtered through Celite, and the filtrate was reduced to several milliliters. Addition of Et_2O caused crystallization to occur. The product was collected by filtration, washed, and dried to give 345 mg (72%) of white crystals, mp 220 °C dec. Anal. ($C_{12}H_{15}NO_2$·HCl) C, H, N.

***cis*- (9) and *trans*-7,10-Dimethoxy-1,2,3,4,4a,5,6,10b-octahydrobenzo[*f*]quinoline Hydrochloride (10).** A mixture of 5.0 g (20 mmol) of the pyrrolidine enamine of ketone **21** and 4.8 g (80 mmol) of acrylonitrile in 50 mL of dioxane was refluxed for 18 h. A mixture of 50 mL of H_2O and 10 mL of HOAc was added, and the mixture was refluxed for 2 h. The organic solvents were removed under vacuum, and the residue was diluted with 50 mL of H_2O and extracted with Et_2O. The Et_2O extracts were washed with 3 N HCl, 10% aqueous NaOH, and H_2O, dried, and evaporated to give 3.3 g of a brown oil. Rapid chromatography on 100 g of silica eluting with 1:1 Et_2O–cyclohexane gave 2.1 g (42%) of pure cyanoethylated tetralone. A solution of 2.1 g of this in 25 mL of EtOH containing 5 mL of HOAc was hydrogenated at 50 psi over 50 mg of PtO_2 for 4 h. The mixture was filtered through Celite, and the filtrate was diluted with 50 mL of 1 N HCl. It was extracted with Et_2O, made alkaline with 10% aqueous NaOH, and extracted again. The basic extracts were dried and treated with ethereal HCl to give 930 mg (41%) of the hydrochloride as a mixture of cis and trans isomers. Benzoylation with benzoyl chloride in a two-phase $CHCl_3$/10% NaOH system gave a quantitative yield of a mixture of *cis*- and *trans*-benzamides, which were reduced with a 10-fold excess of lithium aluminum hydride in ether. The product showed two distinct spots on TLC, which were readily separated by chromatography on 100 g of silica gel eluting with 7:3 cyclohexane–ether containing 2 mL/L of Et_3N. Ten milliliter fractions were taken to give, after workup, 0.50 g of cis (fractions 5–25) and 0.20 g of trans (fractions 30–40) isomers in pure form. Identification of cis and trans isomers was done through analysis of the vicinal coupling constants of the benzylic hydrogens. The benzylic protons of the trans isomer were an AB quartet (δ 3.78) with a chemical-shift difference of 66 Hz (J = 13 Hz), while those of the cis isomer appeared as a broadened singlet (δ 3.8). These values correlate well with previously reported stereochemical studies.[20-22] Hydrogenolysis of the benzyl group of both cis and trans isomers was done over 10% Pd/C at 50 psi for 6 h in MeOH containing concentrated HCl (50% by weight of compound to be hydrogenated). Filtration through Celite, followed by evaporation, gave the product. Crystallization from MeOH/EtOAc gave 65% pure trans isomer, mp 256–259 °C. Anal. ($C_{15}H_{20}NO_2$·HCl) C, H, N. Trituration with acetone of the residue obtained from hydrogenolysis of the *cis*-benzyl isomer gave 84% of pure cis hydrochloride, mp 305 °C. Anal. ($C_{15}H_{20}NO_2$·HCl) C, H, N.

5,8-Dimethoxy-1,2,3,4-tetrahydroisoquinoline (11). Into 150 mL of toluene was dissolved 83 g (0.5 mol) of 2,5-dimethoxybenzaldehyde and 42.5 g (0.5 mol) of aminoacetaldehyde dimethyl acetal. The solution was refluxed for 3 h under a Dean-Stark trap to remove water. The solvent was removed under vacuum to give 127 g (100%) of a pale tan oil. A solution of 27.4 g (0.1 mol) of this in 50 mL of trifluoroacetic anhydride was added dropwise over 1 h to an ice-cold solution of 50 mL of trifluoroacetic anhydride and 36 mL of acetic acid which had been saturated with BF_3. The solution was allowed to warm to room temperature and stirred overnight. It was poured into 500 mL of ice–water, adjusted to pH 9 with 50% NH_4OH, and extracted with three portions of CH_2Cl_2. The combined CH_2Cl_2 layers were extracted twice with 3 N HCl, and the combined aqueous extracts were adjusted to pH 9 with NH_4OH and extracted again with two portions of CH_2Cl_2. The combined basic CH_2Cl_2 extracts were dried and evaporated to leave 15.9 g (79%) of beige crystals. These were dissolved in 50 mL of EtOH and treated with 75 mL of saturated etherial HCl, followed by 400 mL of Et_2O. The resulting crystals were removed by filtration, washed with Et_2O, and dried to give 15.8 g (84%) of bright yellow crystals, mp 206–208 °C. A solution of 15.0 g of this in 400 mL of MeOH was hydrogenated at 60 psi over 200 mg of PtO_2 for 8 h. The mixture was filtered through Celite, and the filtrate was evaporated to give an off-white residue. Crystallization from EtOH gave 9.9 g (65%) of white needles, mp 258–259 °C. Anal. ($C_{11}H_{15}NO_2$·HCl) C, H, N.

6,9-Dimethoxybenzocycloheptan-2-one (15). Into 300 mL of methanol containing 100 mL of water and 0.5 mL of 70% perchloric acid was dissolved 11.4 g (0.045 mol) of 5-(2,5-dimethoxyphenyl)-5-ketopentanoic acid.[24] The solution was hydrogenated over 1 g of 10% Pd/C at 60 °C and 50 psi for 8 h. The mixture was filtered through Celite, and the filtrate was treated with 50 mL of 10% NaOH and refluxed for 4 h. The

methanol was removed under vacuum, and the aqueous phase was extracted with Et_2O, which was discarded. The solution was acidified with 3 N HCl and extracted with Et_2O. The extracts were dried and evaporated to give 8.8 g (82%) of product, bp 130–134 °C (0.5 mm). Cyclization of 5-(2,5-dimethoxyphenyl)-pentanoic acid according to the procedure of Anderson[24] gave the ketone **15** in 45% yield.

5,8-Dimethoxy-1,4-dihydro-1,4-ethanonaphthalene Hydrochloride (16). A mixture of 18.8 g of the adduct between *p*-quinone and 1,3-cyclohexadiene[19] and 10.0 mL of 10% aqueous NaOH was stirred in an ice bath while 25 mL of dimethyl sulfate was added. After addition was complete, the mixture was stirred for 16 h at 25 °C. An additional 50 mL of 10% aqueous NaOH and 15 mL of dimethyl sulfate were added, and the mixture was again stirred for 16 h. The mixture was extracted well with Et_2O, and the extracts were washed, dried, and evaporated to give 17.3 g (80%) of the dimethyl ether **16** as a pale tan oil.

1,1a,6,6a-Tetrahydro-2,5-dimethoxycycloprop[*a*]indene-1-carboxylic Acid (19). Into 100 mL of MeOH was dissolved 6.5 g of 4,7-dimethoxy-1-indanone,[17] and 3 g of $NaBH_4$ was added in portions over 15 min. The mixture was stirred at 25 °C for 30 min, stripped of MeOH, and partitioned between EtOAc and H_2O. The organic layer was separated, washed, dried, and evaporated to give 6.5 g (100%) of the alcohol as a white crystalline solid, mp 70–72 °C. A solution of 5.3 g (27 mmol) of this in 20 mL of pyridine was stirred at 25 °C while 3.54 g (30 mmol) of thionyl chloride was added. The reaction was stirred at 25 °C for 30 min and then refluxed for 2 h. It was poured into 200 mL of Et_2O and washed with H_2O. The organic layer was dried and evaporated onto 5 g of silica gel. It was chromatographed quickly on 60 g of silica using 1:1 hexane–Et_2O to give 2.3 g (48%) of white crystals of **18**, mp 58–59 °C. A suspension of 1.05 g (6 mmol) of this and 200 mg of $CuSO_4$ in 10 mL of xylene was stirred in an oil bath maintained at 75 °C while ethyl diazoacetate in toluene was added dropwise until starting material was consumed (30 mmol of reagent). The reaction was filtered through Celite, and the filtrate was chromatographed on silica gel eluting with 90:10 hexane–ether to give 988 mg (63%) of the exo (**19**) and 236 mg (15%) of the endo adduct (**20**). The ^1H NMR of the endo isomer (**20**) showed a methylene quartet at δ 3.5, while that of the exo isomer (**19**) displayed a quartet at δ 4.3. Hydrolysis with ethanolic sodium hydroxide of the exo ester (**19**) and crystallization of the product from EtOAc gave 640 mg of white crystals, mp 177–179 °C (22% from the 1-indanone). Anal. ($C_{13}H_{14}O_4$) C, H.

(–)-4-Hydroxymorphinanones: Their Synthesis and Analgesic Activity

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A facile procedure is described for the conversion of morphine, via the diphosphate ester derivative **1** followed by catalytic reduction and treatment with Li/NH_3, to 3-deoxy-7,8-dihydromorphine (**3**). Oxidation with benzophenone *tert*-butoxide converted **3** to the ketone **4**, which on treatment with Zn/NH_4Cl formed (–)-4-hydroxymorphinan-6-one **5**. Reaction of **5** with diazomethane formed the methyl ether **6**. The *N*-cyclopropylmethyl analogues of **4** and **5** were also prepared, i.e., **8c** and **9** from **4**. The antinociceptive activity of these compounds was tested. Compounds **5**, **6**, **8c**, and **9** showed potent antiwrithing activity and, based on these data, a structure–activity relationship in morphinans is discussed.

As part of an ongoing program in our laboratories, to explore approaches to a practical synthesis of morphine, codeine, and related opioids, we needed a sample or (–)-4-hydroxymorphinan-6-one (**5**) for final comparison with the totally synthetic material. 4-Hydroxymorphinanones are relatively unexplored and represent an interesting series of morphinanones with a phenolic group at C_4. We achieved their synthesis from morphine and found (–)-4-hydroxymorphinan-6-one (**5**) to possess potent antinociceptive activity. This led us to prepare and examine the *N*-cyclopropylmethyl analogue **9**, in the hope of developing a novel series of mixed agonist/antagonist type analgesics. While our work was in progress, Hsu et al.[1] described a facile synthesis of these compounds, albeit by a different route, and reported their antinociceptive activity.[2] This has prompted us to report our findings at this time. In this paper we report a novel route to the synthesis of 4-hydroxymorphinanones and discuss their antinociceptive activity.

We synthesized the key intermediate 3-deoxy-7,8-dihydromorphine (**3**) from morphine as shown in Scheme I, utilizing the phosphate ester procedure for deoxygenation at C_3. Hsu et al.,[1b] Reden et al.,[3] and Bognar et al.,[4] prepared **3** via the *N*-phenyltetrazolyl ether derivatives. As pointed out by Hsu et al.,[1] compound **3** is an important intermediate, since it can lead to other 3-deoxyopioids,[3] as well as 4-hydroxymorphinanones.[1]

Morphine was treated with diethyl chlorophosphate and anhydrous K_2CO_3 in CH_3CN to give the diphosphate **1**, which was immediately converted to the dihydromorphine **2** by catalytic reduction in ethanol in the presence of (10%) palladium on carbon. Cleavage of the 3-phosphate ester and hydrolysis of 6-ester was achieved by addition of **2** in THF to a 1 N solution of lithium in ammonia and maintaining the blue color for 15 min to give **3** as a colorless glass (75% overall from morphine). Oxidation of **3** by benzophenone–potassium *tert*-butoxide in benzene gave the ketone **4**.[3,5] Treatment with Zn dust and NH_4Cl in refluxing ethanol gave the 4-hydroxymorphinan-6-one (**5**).[1] The corresponding methyl ether **6** was obtained by reaction of **5** with diazomethane.

The *N*-cyclopropylmethyl analogue **9** was prepared from **4** by a four-step process. Thus, reaction of **4** with cyanogen bromide in CH_2Cl_2 solution in the presence of K_2CO_3 gave the *N*-cyano compound **8a**. Hydrolysis to **8b** was accom-

(1) (a) F. Hsu, A. E. Jacobson, K. C. Rice, and A. Brossi, *Heterocycles*, **13**, 259 (1979); (b) F. Hsu, K. C. Rice, and A. Brossi, *Helv. Chim. Acta*, **63**, 2042 (1980); (c) M. D. Rozwadowska, F. L. Hsu, A. E. Jacobson, K. C. Rice, and A. Brossi, *Can. J. Chem.*, **58**, 1855 (1980).

(2) Dr. Brossi has kindly informed us that the antinociceptive activity of these compounds is presently in press and was also presented at various meetings. See also footnotes in ref 1a and 1c.

(3) J. Reden, M. F. Reich, K. C. Rice, A. E. Jacobson, A. Brossi, R. A. Streaty, and W. A. Klee, *J. Med. Chem.*, **22**, 256 (1979).

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(5) Y. Sawa, R. Maeda, and J. Irisawa, U.S. Patent 3 707 470, 1972.

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