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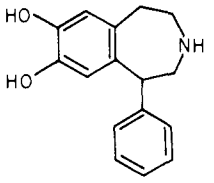
Communications to the Editor

Separation of Potent Central and Renal Dopamine Agonist Activity in Substituted 6-Chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepines

Sir:

An increasing body of experimental data supports the concept that dopamine is an important neurotransmitter and points to the existence of dopamine receptors in peripheral and central nervous system tissues.[1-4] Recent reports from our laboratories[5] have described the unique dopaminergic profile of 1, 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (SK&F 38393).[6] In



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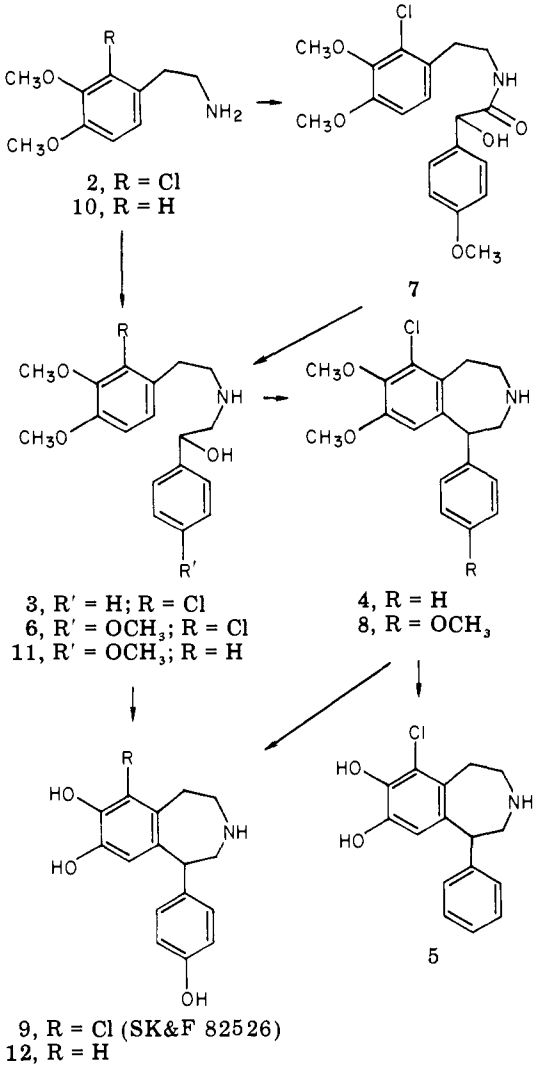
this communication we describe several new 3-benzazepines, some of which show greatly enhanced specficity and potency in activating renal dopamine receptors and which, on peripheral administration to rats and dogs, produce little or no activation of central dopamine receptors.

The preparation of the compounds of interest[7] is shown in Scheme I. Reduction of 2-chloro-3,4-dimethoxyphenylacetonitrile[8] with B_2H_6 in THF gave 2-chlorohomoveratrylamine (**2**) (74%, HBr salt, mp 192–194 °C; trifluoroacetamide, mp 67.5–70 °C). Reaction of **2** with styrene oxide gave the amino alcohol **3** (mp 100–101 °C,

Scheme I



44% isolated yield). Cyclization of **3** with H_2SO_4 in refluxing CF_3COOH gave the benzazepine **4** (HCl salt, mp 243–244 °C, 85% yield), and treatment of **4** with BBr_3 in CH_2Cl_2 gave the catechol **5** (HBr salt, mp 259–260 °C, 86% yield).

The reaction of 4-methoxystyrene oxide with **2** gave the amino alcohol **6** in only 19% yield. In a better sequence, **2** was heated with methyl 4-methoxymandelate to give the mandelamide **7**, which was reduced without purification by B_2H_6 in THF to give the amino alcohol **6** (mp 118.5–121 °C, 68% yield). Cyclization of **6** with H_2SO_4 in CF_3COOH at 25 °C gave **8** (mp 143.5–145 °C, 68% yield). Cleavage of the ether groups of **8** using BBr_3 in CH_2Cl_2 gave the

(1) (a) L. I. Goldberg, *Pharmacol. Rev.*, **24**, 1 (1972); (b) J. G. Cannon, *Adv. Biosci.*, **20**, 87–94 (1978).
(2) L. L. Iverson, *Science*, **188**, 1084 (1975).
(3) P. E. Setler, R. G. Pendleton, and E. Finlay, *J. Pharmacol. Exp. Ther.*, **192**, 702 (1975).
(4) (a) J. W. Kebabian and D. B. Calne, *Nature (London)*, **277**, 93 (1979); (b) I. Creese and S. H. Snyder, *Eur. J. Pharmacol.*, **50**, 459 (1978); (c) I. Creese, D. R. Burt, and S. H. Snyder, *Science*, **192**, 481 (1976).
(5) (a) P. E. Setler, H. M. Sarau, C. L. Zirkle, and H. L. Saunders, *Eur. J. Pharmacol.*, **50**, 419 (1978); (b) R. G. Pendleton, L. Samler, C. Kaiser, and P. T. Ridley, *Eur. J. Pharmacol.*, **51**, 19 (1978); (c) R. A. Hahn and J. R. Wardell, Jr., *J. Cardiovasc. Pharmacol.*, submitted.
(6) A. Walter and W. K. Chang, U.S. Patent 3 393 192 (July 1966) to Schering Corp. This compound was originally prepared in our laboratories by Dr. S. T. Ross.
(7) All new compounds gave satisfactory analyses for C, H, and N and were further characterized by NMR and in most instances by MS.
(8) A. Paraulkar, A. Burger, and D. Aures, *J. Med. Chem.*, **9**, 738 (1966).

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Table I. Dopamine Agonist Activity

	renal vasodilator activity					central dopaminergic activity[g,h]		
			selectivity ratios			contralateral rotation in lesioned rat		rat striatal adenylate cyclase:
compd[a]	ED_{15} ↓RVR, μg/kg iv	av max % ↓RVR	IVR (ED_{30})/ RVR (ED_{15})	MABP (ED_{20})/ RVR (ED_{15})	HR (ED_{20})/ RVR (ED_{15})	RD_{500}, mg/kg ip	RD_{500}, μg/rat ic	EC_{50}, M
1 (SK&F 38393)	31[b] (3)[f]	19	15	10		0.7 (0.5-1.0)	0.18 (0.03-0.91)	8×10^{-8}[b]
dopamine	2.7 (3)[f]	36	56	113	141		0.10[c] (0.08-1.3)	3.5×10^{-6}
5	3.5 (2)[f]	39	628	>1734	108	0.30 (0.21-0.75)	0.22 (0.07-1.55)	1×10^{-8}
12	[d]					10 mg/kg, 13 ± 4 turns	1 μg = 532 ± 147	ca. 5×10^{-7}
9 (SK&F 82526)	0.3 (5)[f]	59	>6072	>6072	>6072	10 mg/kg,[e] 14 ± 7 turns	0.5[e] (0.4-0.8)	1.8×10^{-8}[e]

[a] Tested as the hydrobromide salt unless otherwise noted. [b] Tested as the hydrochloride salt. [c] Treated with 1 mg/kg ip tranylcypromine (monoamine oxidase inhibitor) 3 h before test. [d] When tested in the usual protocol ($N = 4$), significant increases in renal and iliac resistance and blood pressure were seen. [e] Tested as the methanesulfonate salt. [f] Number of dogs used in test. [g] See ref 5a for details of methodology. [h] 95% confidence limits are indicated in parentheses below values.

catechol **9** (HBr salt, mp 277 °C dec, 90% yield; CH_3SO_3H salt, mp 274 °C dec).

Reaction of 4-methoxystyrene oxide with homoveratrylamine (**10**) gave the trimethoxy amino alcohol **11** (mp 92 °C, 33% yield), which was converted directly to the trihydroxybenzazepine **12** by refluxing 48% HBr (HBr salt, mp 287–289 °C, 70% yield).

Vasodilator activity was measured in anesthetized dogs surgically prepared for electromagnetic measurement of renal and iliac artery blood flows. Blood pressure was measured from the carotid artery, and drugs were infused into an antecubital vein. Heart rate was recorded by a cardiotachometer triggered by the electrocardiogram. Vascular resistance was calculated as the ratio of mean arterial blood pressure to mean blood flow. Cumulative dose–response data were obtained by infusing the drug at progressively increasing (usually threefold) concentrations, each dose level being infused for 5 min. The following changes were determined to be the minimum necessary for statistical significance ($p = 0.95$): renal vascular resistance (RVR), 16%; mean arterial blood pressure, ±6%; iliac vascular resistance (IVR), ±24%; and heart rate (HR), ±9%. For comparison, the potency for each compound is expressed as the average minimum cumulative dose which decreases RVR by 15%. The maximum renal vasodilator effect is expressed as the average maximum percent decrease in RVR attainable with the compound. The selectivity ratios are the separation between RVR–ED_{15} and doses producing (1) a 30% change in IVR, (2) a 20% increase in MABP, and (3) a 20% change in HR. The procedures and parameters used to evaluate the central dopaminergic activity are described in a previous report.[5a]

A comparison of some of the effects of dopamine, SK&F 38393, and the new benzazepines **5**, **9**, and **12** on the renal vasculature and the central nervous system is shown in Table I. The 6-chloro analogue, **5**, is about nine times as potent as **1** and causes the same maximal decrease in renal vascular resistance as dopamine, in contrast to **1** which behaves as only a partial agonist in this sytem. Compound **5** is equipotent to **1** and dopamine in causing contralateral rotation in the lesioned rat on intracaudal administration but, surprisingly, is 8 times more potent than **1** and 350 times more potent than dopamine in stimulating rat striatal adenylate cyclase.

The 4′-hydroxy analogue of **5**, SK&F 82526 (**9**), is 100 times more potent than **1** and 9 times more potent than dopamine as a renal vasodilator. It produces a maximal renal vasodilation which is 50% greater than the maximal renal vasodilation achievable with dopamine. In the face of very substantial dose-related decreases in renal vascular resistance with **9**, it is noteworthy that as a consequence of the renal selectivity only very modest changes in mean arterial blood pressure and heart rate are seen. At increased doses, **9** produces a very modest hypotension in contrast to the potent hypertensive effects of dopamine. Compound **9** is essentially inactive in the rat rotation test when administered intraperitoneally but is one-fifth as active as dopamine on intracaudal administration. Finally, **9** is 190 times as potent as dopamine as a stimulant of rat striatal adenylate cyclase. The maximal stimulation was approximately 80% of that produced by 50 μM dopamine and at near maximal stimulating concentrations was antagonized in a concentration-dependent manner by dopamine antagonists such as haloperidol, chlorpromazine, and bulbocapnine.

The 4′-hydroxy analogue of **1** (**12**), which lacks the 6-chloro substituent present in **9**, is inactive as a renal vasodilator at the doses tested. Although **12** produces significant contralateral rotation in the lesioned rat when administered intracaudally, it is not active when administered intraperitoneally.

It seems clear that the unusual renal vasodilator activity of **9** is the result of the unique contribution of both the 6-chloro and the 4′-hydroxy substituents. One might speculate that the 6-chloro substituent enhances binding at the receptor in a conformation which induces maximum activation of the renal receptor. Alternatively one may speculate that the 4′-hydroxy group enhances polarity which decreases entry into lipophilic drug compartments and thus promotes higher concentration in the kidney. Some potent dopamine antagonists in related benzazepines are discussed in an accompanying communication from our laboratories.[9]

The data presented in Table I suggest that **9** is a potent adenylate cyclase mediated dopamine agonist which does not cross the blood–brain barrier and thus does not exert

(9) C. Kaiser, Fadia E. Ali, William E. Bondinell, Martin Brenner, Kenneth G. Holden, Thomas W. Ku, Hye-Ja Oh, Stephen T. Ross, Nelson C. F. Yim, Charles L. Zirkle, Richard A. Hahn, Henry M. Sarau, Paulette E. Setler, and Joe R. Wardell, Jr., *J. Med. Chem.*, **23**, following communication in this issue (1980).

significant central dopaminergic activity. The potent and specific renal vasodilator effects of this coumpound suggest that it might be useful in reversing the increased renal vascular resistance seen in many hypertensive subjects. In addition, it could be of utility in other disease states in which renal ischemia is a prominent component.

Acknowledgment. We thank Paul Woodward, James M. Smith, Maryann Malesky, Cynthia Smith, and Joseph McDevitt of Biological Research for expert technical assistance.

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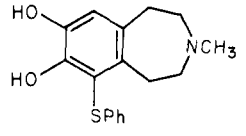
6-(Phenylthio)-Substituted 2,3,4,5-Tetrahydro-1*H*-3-benzazepines, a Novel Class of Dopamine Receptor Antagonists and Neuroleptics

Sir:

Although the activity of antipsychotic agents is generally associated with their influence on dopaminergic neurons,[1] their structural relationship[2] to the neurotransmitter is not readily apparent.[3] In this communication we describe a novel class of dopamine receptor antagonists and neuroleptics, 2,3,4,5-tetrahydro-7,8-dihydroxy-6-(phenylthio)-1*H*-3-benzazepines, e.g., 1 (SK&F 83742), that clearly incorporate the structure of dopamine within their molecular framework.



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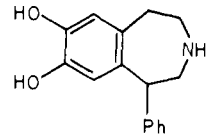

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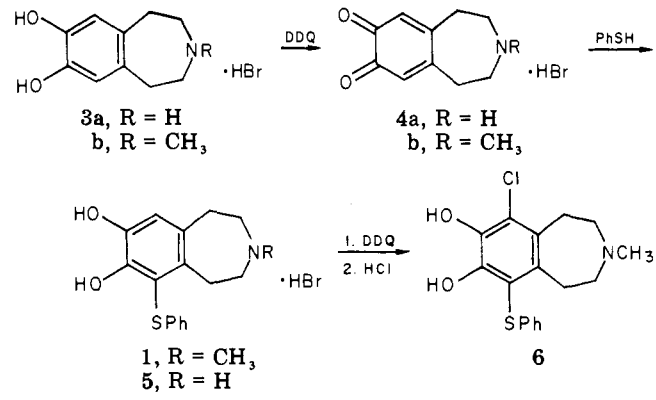
These agents were identified in an extensive study of relatives of 2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (**2**, SK&F 38393), a potent agonist of both central[4] and peripheral[5] dopamine receptors. According to a recent subclassification[6] of central dopamine receptors, **2** is selective for the D-1 subtype. Conformationally, **2** differs from most dopamine receptor agonists which are analogues of dopamine constrained in an extended (anti, trans) form.[7-9] The tetrahydroazepine ring of **2**, although allowing considerable flexibility, imparts some conformational restraints. Thus, the spatial relationship of the nitrogen atom and the fused aromatic ring of **2** can vary from a nearly folded (fully eclipsed, cis) orientation[10] to a partially eclipsed (anticlinal) one; however, the extended (trans) form is prohibited.[11] This uniqueness, coupled with the partial agonism exhibited by **2** in stimulating adenylate cyclase,[4] prompted our investigation of related structures to identify potentially novel and selective dopamine receptor agonists and antagonists. Preliminary accounts of these studies are presented here and in the preceding communication.[12]

Scheme I



6-(Phenylthio)-substituted benzazepines were prepared as outlined in Scheme I.[13] Oxidation of **3a**[14] and **3b** (obtained from the corresponding dimethoxybenzazepine[14] by refluxing in 48% aqueous HBr, 47% yield, mp 230-233 °C, after recrystallization from MeOH-Et_2O) with 2,3-di-

(1) S. H. Snyder, *Am. J. Psychiatry*, **133**, 197 (1976).
(2) C. Kaiser and P. E. Setler, in "Burger's Medicinal Chemistry", 4th ed., Part 3, M. E. Wolff, Ed., Wiley-Interscience, New York, 1980, Chapter 56.
(3) A similar mode of receptor interaction has been suggested for chlorpromazine and the trans form of dopamine on the basis of possible overlap of the amino group and other structural features [A. S. Horn and S. H. Snyder, *Proc. Natl. Acad. Sci. U.S.A.*, **68**, 2325 (1971)]. Antipsychotic drugs of the butaclamol type have been employed to map the central dopamine receptor. This study has resulted in the proposal of a receptor model [A. H. Philipp, L. G. Humber, and K. Voith, *J. Med. Chem.*, **22**, 768 (1979)]. In neither chlorpromazine nor butaclamol, however, is the dopamine framework obvious.
(4) P. E. Setler, H. M. Sarau, C. L. Zirkle, and H. L. Saunders, *Eur. J. Pharmacol.*, **50**, 419 (1978).
(5) R. G. Pendleton, L. Samler, C. Kaiser, and P. T. Ridley, *Eur. J. Pharmacol.*, **51**, 19 (1978).
(6) J. W. Kebabian and D. B. Calne, *Nature (London)*, **277**, 93 (1979).
(7) (a) P. H. Volkman, J. D. Kohli, L. I. Goldberg, J. G. Cannon, and T. Lee, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 3602 (1977); (b) L. I. Goldberg, J. D. Kohli, A. N. Kotake, and P. H. Volkman, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **37**, 2396 (1978).
(8) J. G. Cannon, *Adv. Biosci.*, **20**, 87-94 (1978).
(9) G. N. Woodruff, A. Davis, C. D. Andrews, and J. A. Post, in "Recent Advances in Receptor Chemistry", F. Gualtieri, M. Giannella, and C. Melchiorre, Eds., Elsevier/North-Holland Biomedical Press, Amsterdam, 1979, pp 165-188.
(10) Several catecholic tetrahydroisoquinolines, e.g., (-)-1,2-dihydroxyaporphine [R. J. Miller, P. H. Kelly, and J. L. Neumeyer, *Eur. J. Pharmacol.*, **35**, 77 (1976)] and (*S*)-(-)-salsolinol [P. Seeman, M. Titeler, J. Tedesco, P. Weinrich, and D. Sinclair, *Adv. Biochem. Psychopharmacol.*, **19**, 167-176 (1978)], in which the aromatic ring and basic nitrogen are rigidly fixed in a cis orientation apparently do not interact with dopamine receptors.
(11) J. W. Wilson, "Program and Abstracts", National Medicinal Chemistry Symposium of the American Chemical Society, 16th, Kalamazoo, MI, June 18-22, 1978, American Chemical Society, Washington, D.C., 1978, p 155.
(12) J. Weinstock, J. W. Wilson, D. L. Ladd, C. K. Brush, F. R. Pfeiffer, G. Y. Kuo, K. G. Holden, N. C. F. Yim, R. A. Hahn, J. R. Wardell, Jr., A. J. Tobia, P. E. Setler, H. M. Sarau, and P. T. Ridley, *J. Med. Chem.*, **23**, preceding communication in this issue (1980).
(13) All new compounds for which melting points are given afforded satisfactory analyses for C, H, and N. NMR and MS were determined for all compounds; they were considered consistent with the assigned structures.
(14) B. Pecherer, R. C. Sunbury, and A. Brossi, *J. Heterocycl. Chem.*, **8**, 779 (1971).

0022-2623/80/1823-0975$01.00/0