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Communications to the Editor

6-Chloro-2,3,4,5-tetrahydro-3-methyl-1*H*-3-benzazepine: A Potent and Selective Antagonist of α_2-Adrenoceptors

Sir:

During the last decade much evidence has accumulated that supports the concept that in addition to the classical postsynaptic α_1-adrenoceptors that mediate the responses of effector organs to norepinephrine, there are also α_2-receptors located presynaptically on noradrenergic nerve terminals.[1] These receptors are part of a negative feedback mechanism that modulates the release of norepinephrine in the periphery and the central nervous system. More generally, these α_2-receptors can be differentiated from the α_1-receptor by their specificity toward a series of agonists and antagonists. This pharmacological classification is independent of anatomical distribution.[2,3] Such a 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. We report here the synthesis and preliminary characterization of a novel and selective α_2-antagonist, 6-chloro-2,3,4,5-tetrahydro-3-methyl-1*H*-3-benzazepine (SK&F 86466).

Chemistry. This compound was prepared in five steps in an overall yield of 59% from commercially available *o*-chlorophenylacetic acid as shown in Scheme I.[4]

Treatment of *o*-chlorophenylacetic acid (1) in toluene with excess thionyl chloride and several drops of DMF gave, after removal of solvent, a quantitative yield of the corresponding acid chloride, which was used without further purification. This acid chloride, in methylene chloride, was aminated with excess 2-(methylamino)-ethanol to give 80% of 2-chloro-*N*-(2-hydroxyethyl)-*N*-methylphenylacetamide (2) as a crystalline solid, mp 78–79 °C (EtOAc). Reduction of amide 2 with diborane in THF yielded amino alcohol 3, in 93% yield as a colorless oil. Treatment of 3 in chloroform with phosphorous pentachloride in chloroform yielded 4, mp 115–117 °C (EtOH–Et_2O). This was cyclized at 175 °C for 4 h in a melt of aluminum chloride and ammonium chloride to give 80% of 5 as a white crystalline hydrochloride, mp 268 °C dec, after repeated crystallization from MeOH–EtOAc.[5]

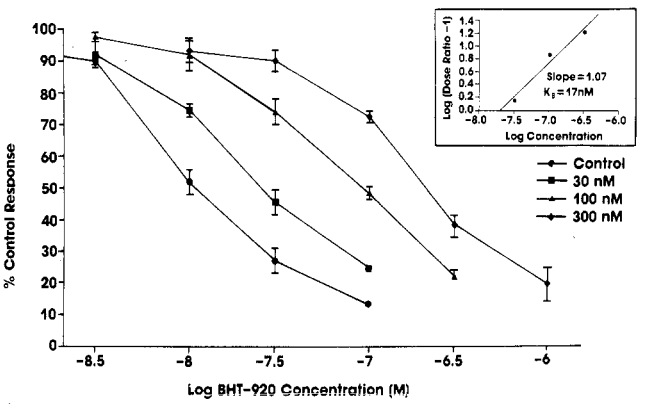
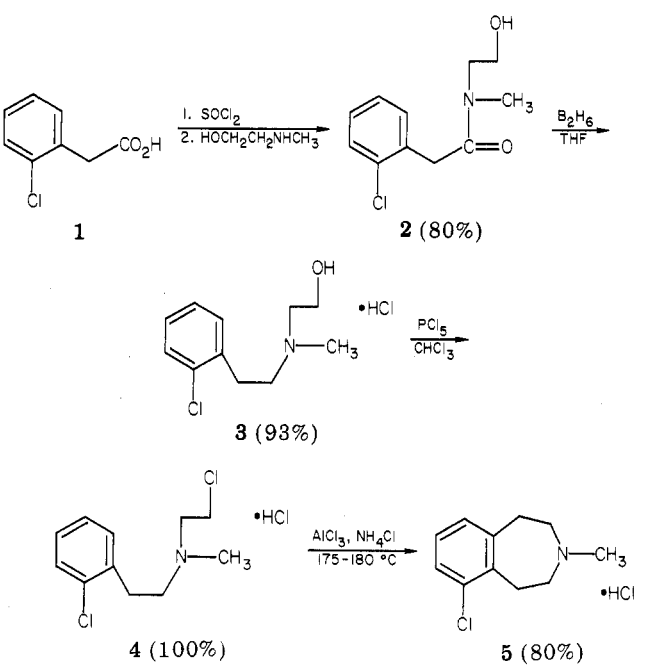


Figure 1. Antagonism of BHT 920 induced inhibition of neurotransmission in the guinea pig atrium by **5**. Each curve represents the mean of three experiments.[6]

Scheme I



Biology. Activation of α_2-receptors located on prejunctional sympathetic nerve terminals activates a negative

(1) For example, see S. Z. Langer, *Trends Neurosci.*, **3**, 110 (1980). K. Starke, *Rev. Physiol., Biochem., Pharmacol.*, **71**, 1 (1977).

(2) S. Berthelsen and W. A. Pettinger, *Life Sci.*, **21**, 595 (1977). K. Starke and S. Z. Langer, *Adv. Biosci.*, **18**, 1–3. J. E. S. Wikberg, *Acta Physiol. Scand., Suppl.*, **468**, 1 (1979).

(3) α_2-Adrenoceptors are also found postsynaptically in vasculature, as well as in a variety of noninnervated tissues. For an excellent general review on the subject, see P. B. M. W. M. Timmermans and P. Van Zwieten, *J. Med. Chem.*, **25**, 1389 (1982).

(4) IR and NMR spectra for all compounds were routine and supported the assigned structure. C, H, and N analyses were within 0.4%.

(5) Cyclization under these conditions often produced as a side product 10–20% of the 7-chloro isomer. This may form by opening of the seven-membered ring and subsequent reclosure. This unwanted isomer can be removed by repeated crystallization from MeOH–EtOAc or by preparative chromatography.

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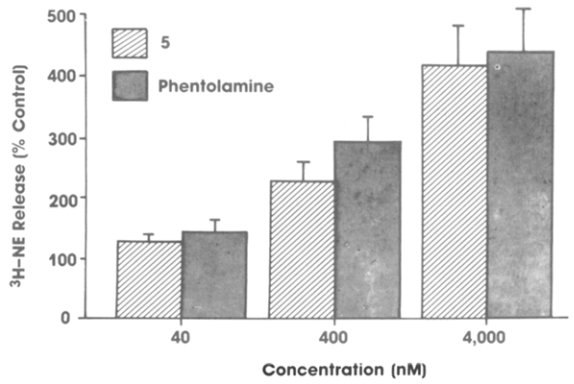

Figure 2. Effect of **5** and phentolamine on stimulation-evoked release of [^{3}H]norepinephrine (NE) from the dog splenic artery. Stimulation at 1.5–2 Hz for 120 s. Each bar represents the mean of four experiments plus or minus the SEM.

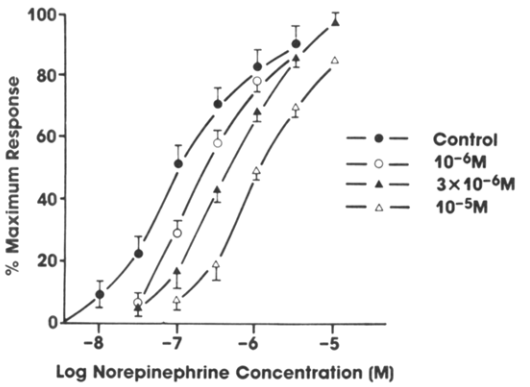

Figure 3. Antagonism of the constrictor response to norepinephrine in the isolated rabbit ear artery segment by **5**. Mean K_B value = 900 nM. Each curve represents the mean of five experiments.[6]

feedback cycle that shuts off the further release of norepinephrine. This results in a decrease in the postsynaptic effector response mediated by released norepinephrine. An in vitro physiological system to measure presynaptically mediated α effects is the isolated guinea pig atrium.[6] In this model BHT 920,[7] a presynaptic α_2-agonist, activates α_2-receptors to inhibit transmitter release. A concentration-related inhibition of the response to sympathetic nerve stimulation is observed in the presence of BHT 920. The EC_{50} for BHT 920 as an agonist in this preparation is 1.0×10^{-8} M. Compound **5** is able to antagonize this inhibitory effect of BHT 920 in a dose-dependent fashion at low concentrations. It is a potent, competitive inhibitor of BHT 920 induced depression of neurotransmission in the isolated guinea pig atrium with a dissociation constant (K_B) of 17 nM (Figure 1). In this model phentolamine, a nonselective α-antagonist has a K_B of 7 nM, which is in good agreement with K_B values reported for phentolamine as an antagonist of a variety of α_2-adrenergic responses.[8,9]

The physiological consequence of blockade of presynaptic α_2-receptors is an increased release of norepinephrine from adrenergic varicosities per nerve impulse. This can be measured by determining the ability of an agent to increase the amount of radiolabeled norepinephrine released upon electrical stimulation of sympathetic nerve terminals. Compound **5** increased the release of [^{3}H]norepinephrine from electrically stimulated dog splenic arteries with an EC_{100} of 210 nM. The efflux of [^{3}H]norepinephrine is dose related and comparable to that shown by phentolamine (Figure 2).

As an index of α_1-adrenoceptor blockade we examined the antagonism of the constrictor response to norepinephrine in the isolated rabbit ear artery.[6] In this model, **5** was significantly less potent than in those models whose responses are mediated by α_2-receptors. This compound was far less effective an antagonist of the postsynaptic α_1 response to norepinephrine than it was as an antagonist of the presynaptic α_2 response mediated by BHT 920 in the guinea pig atrium. Compound **5** blocks the norepinephrine constrictor response in the rabbit ear artery in a competitive fashion with a K_B of 900 nM (Figure 3). Based on these data and those obtained in the guinea pig atrium, **5** shows a selectivity ratio [K_B (α_1)/K_B (α_2)] of 53. In these preparations, phentolamine shows a selectivity ratio of 16, while yohimbine demonstrates a ratio of 165. Compound **5** is representative of a new class of potent and selective α_2-receptor antagonists which may have clinical utility.[10]

Registry No. **1**, 2444-36-2; **2**, 86129-51-3; **3**, 86129-52-4; **4**, 86129-53-5; **5**, 86129-54-6; **5** (free base), 73943-10-9.

(6) J. P. Hieble and R. G. Pendleton, *Naunyn-Schmiedeberg's Arch. Pharmacol.*, **309**, 217 (1979).
(7) U.S. Patent 3 804 849, 2-amino-6-allyl-5,6,7,8-tetrahydro-4*H*-thiazolo[4,5-*d*]azepine dihydrochloride.
(8) R. F. Furchgott, "Handbook of Experimental Pharmacology—New Series", O. Fichler, A. Farah, H. Hecken and A. D. Welch, Eds., Springer, New York, 1972, pp 283–335.
(9) J. C. Doxey, C. F. C. Smith, and J. M. Walker, *Br. J. Pharmacol.*, **60**, 91–96.
(10) Detailed pharmacological characterization of **5** will appear in a series of separate publications.

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