Stereochemical Studies of Adrenergic Drugs. Optically Active Derivatives of Imidazolines

Duane D. Miller,* Fu-Lian Hsu, Robert R. Ruffolo, Jr., and Popat N. Patil

Division of Medicinal Chemistry and Pharmacology, College of Pharmacy, The Ohio State University, Columbus, Ohio 43210.
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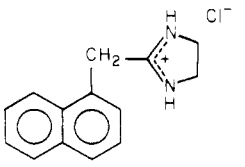
The synthesis of (*R*)-(+)-4-methyl-2-(1-naphthylmethyl)imidazoline hydrochloride (**2**) and (*S*)-(−)-4-methyl-2-(1-naphthylmethyl)imidazoline hydrochloride (**3**) is presented. The synthesis involves the preparation of (*R*)-(+)- and (*S*)-(−)-1,2-diaminopropane dihydrochloride and then allowing the appropriate diaminopropane to react with ethyl 1-naphthyliminoacetate hydrochloride in the presence of triethylamine. The parent compound, naphazoline, is a potent α-adrenoreceptor agonist (−log ED_{50} = 7.22), whereas the methylated derivatives, **2** and **3**, were moderately potent antagonists (pA_2 = 5.6 and 5.8, respectively) of the α-adrenoreceptor. Compounds **2** and **3** also produced blockade of the response to histamine on the rabbit aorta, but at concentrations approximately 20 times higher than necessary to produce equal blockade of the α-adrenoreceptor.

An important group of drugs capable of interacting with α-adrenergic receptors other than the well-known phenethanolamines are the imidazoline derivatives.[1-3] It has been shown that optical isomers of a variety of substituted phenethanolamines show difference in activation of α- and β-receptors. Studies concerning the configurational aspects of phenethanolamines play an important role in gaining a better understanding of the mechanism of action of adrenergic drugs.[4] Recently, several reports have appeared on structure–activity relationships of imidazoline derivatives.[5-8] It is particularly striking that no stereochemical studies have been carried out with imidazoline derivatives in isolated adrenergic systems. We have initiated a program of studying optically active imidazoline derivatives possessing either agonist or antagonist activity in adrenergic systems. This report is concerned with the preparation of optically active derivatives of naphazoline hydrochloride (**1**), a potent α-adrenergic agonist.[1-3] The optically active 2,4-disubstituted imidazoline derivatives that have been prepared and examined in α-adrenergic tissues are **2** and **3**.



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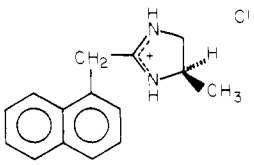

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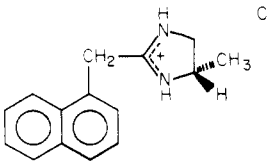

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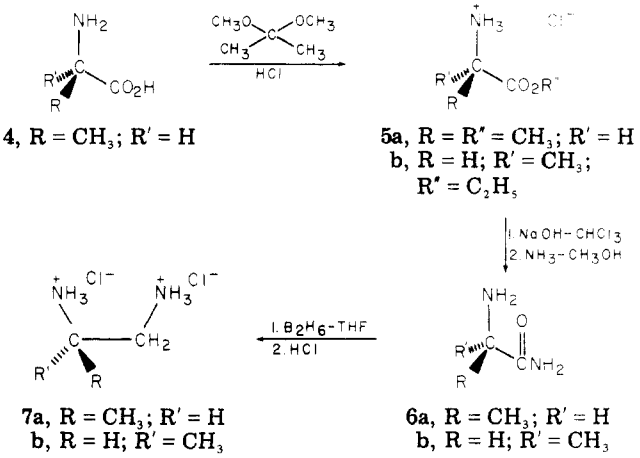
Chemistry. The optically active 1,2-propylenediamines **7a** and **7b** were prepared by the synthetic route outlined in Scheme I rather than by conventional resolution.[9,10] The preparation of the intermediate optically active alanine amides, **6a** and **6b**, was carried out analogously to the method of Yang and Riring.[11] Diborane reduction of **6a** or **6b** in THF[12] followed by the addition of MeOH and dry HCl gave the desired optically active 1,2-diaminopropane dihydrochlorides, **7a** and **7b**, respectively.[9] This method proved to be very useful for preparing the optically active 1,2-diamino derivatives from amino acids of known absolute configurations.

The preparation of **2** and **3** was carried out as illustrated in Scheme II. 1-Naphthylacetonitrile (**8**) was converted to the imidate ester **9** according to the procedure of

Scheme I



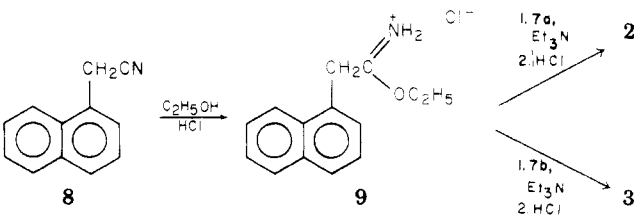
4, R = CH_3; R′ = H

5a, R = R″ = CH_3; R′ = H
b, R = H; R′ = CH_3; R″ = C_2H_5

7a, R = CH_3; R′ = H
b, R = H; R′ = CH_3

6a, R = CH_3; R′ = H
b, R = H; R′ = CH_3

Scheme II



8 **9**

McElvain and Stevens.[13] The imidate was then allowed to react with optically active **7a** and **7b** via a modification of the procedure of King and Acheson[14] (see Table I).

Biological Results. Neither compound **2** nor **3** possessed agonist activity on the rabbit aorta when examined in concentrations as high as 10^{-3} M. Conversely, the parent compound **1** was a potent agonist on α-adrenoreceptors with an ED_{50} of 6×10^{-8} M. Both compounds **2** and **3** possess moderate α-adrenoreceptor blocking activity as evidenced by parallel shifts in the dose–response curve to the agonist, phenylephrine (Figure 1). Figure 2 is a Schild plot[15] for compounds **2** and **3**. The intercept along the abscissa is the pA_2 (i.e., negative log of the molar concentration of antagonist that causes a two-fold shift to the right in the dose–response curve of an agonist) which is a measure of antagonist activity. The pA_2 values of 5.60 and 5.76 for compounds **2** and **3**, respectively, indicate an apparent lack of stereoselectivity. The slopes on the Schild plot are very close to the theoretical value of one indicating that blockade is competitive.

Since compounds **2** and **3** each possess an imidazoline ring, their ability to block the response to histamine was examined. As shown in Figure 3, both compounds possess

Table I. Physical Properties of 1,2-Diaminopropane and Imidazolines

Compd	Final crystn solvent	Mp, °C	$[\alpha]^{28}$, deg		Concn, % (solvent)
			Na_{589}	Hg_{578}	
(*R*)-(+)-7a	MeOH + Et_2O	236-238	+3.96	+4.06	0.96 (H_2O)
(*S*)-(−)-7b	MeOH + Et_2O	236-238	−4.0	−4.12	0.85 (H_2O)
(*R*)-(+)-2	Abs EtOH + Et_2O	187-188.5	+53.40	+56.13	1.06 (MeOH)
(*S*)-(−)-3	Abs EtOH + Et_2O	187-188.5	−52.58	−55.38	0.93 (MeOH)

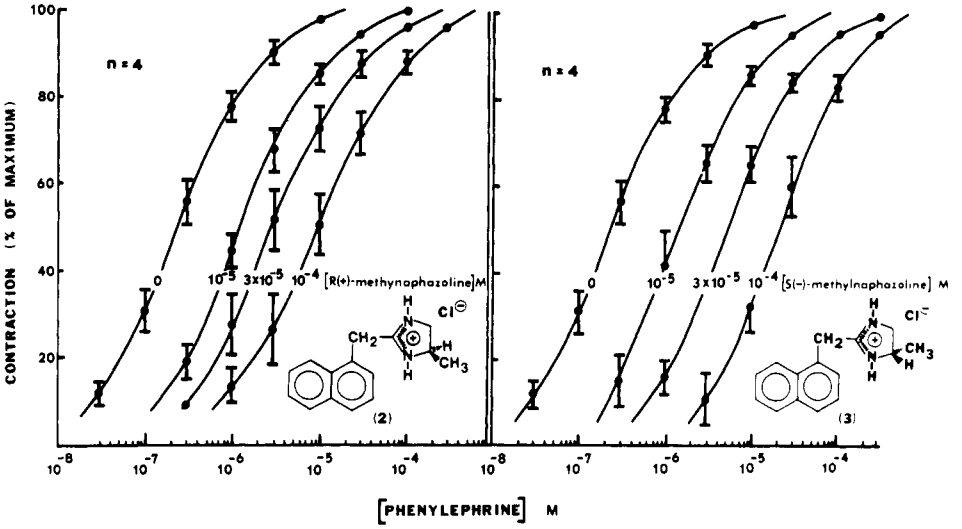


Figure 1. Cumulative log dose-response curves for phenylephrine in the absence and presence of various concentrations of (*R*)-(+)- and (*S*)-(−)-methylnaphazoline (compounds 2 and 3, respectively). The data are expressed as percent of the maximum contraction to phenylephrine. Each point is the mean of four observations and the vertical bars represent the standard error of the mean.

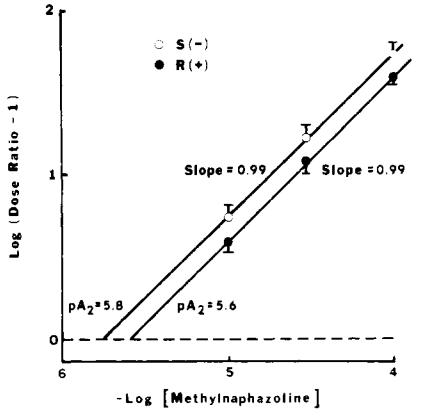


Figure 2. Schild plot for the data presented in Figure 1. The dose ratios were calculated by dividing the ED_{50} of a dose-response curve to phenylephrine in the presence of (*R*)-(+)- or (*S*)-(−)-methylnaphazoline by the ED_{50} of the control dose-response curve to phenylephrine. The intercept along the abscissa is the pA_2 which is the negative log of the molar concentration of antagonist that causes a twofold shift to the right in the dose-response curve to an agonist. Each point is the mean of four observations and the vertical bars are the standard error of the mean.

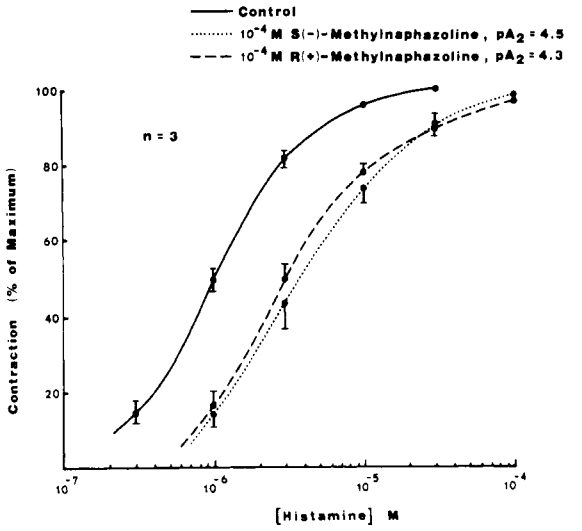


Figure 3. Cumulative log dose-response curve for histamine in the presence of 10^{-4} M concentrations of (*R*)-(+)- and (*S*)-(−)-methylnaphazoline. The data are expressed as percent of the maximum contraction to histamine. The pA_2 values were obtained from the dose ratios and the following equation: $pA_2 = -\log([\text{methylnaphazoline}]/[\text{dose ratio} - 1])$. Each point is the mean of three observations and the vertical bars represent standard error of the mean.

weak antihistamine activity in the rabbit aorta. The pA_2 values for compounds 2 and 3 are 4.3 and 4.5, respectively, indicating an approximate 20-fold higher affinity for α-adrenoreceptors than for the H_1-histaminergic receptor. As with the α-adrenoreceptor, no apparent stereoselectivity could be detected with the histamine receptors.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Spectral data were obtained using a Perkin-Elmer 257 and Beckman 4230 infrared spectrophotometer and a Varian A-60A nuclear magnetic resonance spectrometer. The optical rotations were obtained by using a Perkin-Elmer 240 polarimeter. Analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Analytical results for elements indicated were within ±0.4% of the theoretical values.

(2*R*)-Alanine Methyl Ester Hydrochloride (5a). To a suspension of (2*R*)-alanine, 2 g (22.4 mmol), in 230 ml of 2,2-dimethoxypropane was added 23 ml of HCl (37%). The mixture was stirred for 18 h at room temperature. The solvent was evaporated and the resulting residue was dried under high vacuum

to give a solid which was recrystallized from MeOH–Et_2O to yield the hydrochloride salt: 2.9 g (92%); mp 109–111 °C (lit.[18] mp 109–110 °C).

(2*R*)-Alanine Amide (6a). To the free base of **5a**, 16.59 g (0.1512 mol), was added a solution of 25 ml of MeOH saturated with NH_3 at 0 °C. The mixture was allowed to stand at room temperature and monitored by TLC. After 4 days the reaction was completed and the MeOH and excess NH_3 were evaporated to give a yellow oil, 8.66 g (65%), which solidified upon standing: mp 74–76 °C (lit.[11] mp 72–74 °C).

(2*S*)-Alanine Amide (6b) was prepared according to the above procedure except **5b** was used as a starting material: mp 74–76 °C.

(*R*)-(+)-1,2-Diaminopropane Dihydrochloride (7a). A 250-ml, three-necked flask equipped with a magnetic stirring bar, dropping funnel, thermometer, and reflux condenser was flushed with dried N_2 and maintained under a slight positive N_2 pressure. To a solution of **6a**, 1 g (11.35 mmol), in 25 ml of THF was added dropwise 57 ml of B_2H_6 (1 M in THF) at 20–25 °C over a 1-h period. The solution was stirred for another 1 h at 20–25 °C and was then refluxed for 6 h. The solution was cooled to 20–25 °C and MeOH (15 ml) was added dropwise at a rate such that the reaction temperature did not exceed 30 °C. The resulting clear solution was allowed to stand overnight at room temperature. After cooling to below 10 °C in an ice bath, dry HCl was bubbled slowly into the solution with stirring until solution reached pH 2. The white solid was collected, washed with ether, and recrystallized from MeOH–Et_2O to give **7a**: 1.13 g (68%); mp 236–238 °C (lit.[9] mp 238.5 °C). Anal. ($C_3H_{12}N_2Cl_2$) C, H, N.

(*S*)-(−)-1,2-Diaminopropane Dihydrochloride (7b). The procedure was identical with that for the preparation of **7a**. **7b** showed melting point and ir and NMR spectral properties identical with **7a**. Anal. ($C_3H_{12}N_2Cl_2$) C, H, N.

Ethyl 1-Naphthyliminoacetate Hydrochloride (9). A mixture of **8**, 7 g (41.86 mmol), and absolute EtOH, 2.5 g (54.26 mmol), was cooled in an ice bath and treated with dry HCl until 1.7 g had been absorbed. The solution was kept in a refrigerator for 4 days. The resulting viscous liquid was treated with an equal volume of absolute Et_2O. The gummy hydrochloride was then washed with Et_2O and stored in a desiccator with KOH pellets without further purification.

(*R*)-(+)-4-Methyl-2-(1-naphthylmethyl)imidazoline Hydrochloride (2). A cold solution of **9**, 2.62 g (10.5 mmol), in 8 ml of MeOH was added to **7a**, 1.5 g (10.2 mmol), and Et_3N, 2.28 g (22.5 mmol), in 15 ml of cold MeOH and the resulting mixture was refluxed for 1 h. The solution was evaporated to give a semisolid, to which 20 ml of H_2O and NaOH, 920 mg (23 mmol), were added. The mixture was then taken up in $CHCl_3$ and washed with H_2O. The $CHCl_3$ layer was then dried (Na_2SO_4) and evaporated to yield an oil which was distilled to give **2**: 1.86 g (80.5%); bp 163–166 °C (0.18 mm). To a solution of Et_2O saturated with gaseous HCl was added a solution of **2** as the free base in the minimum amount of $CHCl_3$. The hydrochloride salt **2** was separated and recrystallized from absolute EtOH–Et_2O after pretreatment with a small amount of charcoal to give a white solid: mp 187–188.5 °C; CD $[\theta]_{216}$ +22 370° (*c* 0.102, MeOH). Anal. ($C_{15}H_{17}N_2Cl$) C, H, N.

(*S*)-(−)-4-Methyl-2-(1-naphthylmethyl)imidazoline Hydrochloride (3). The procedure was the same as for the preparation of **2**. The crude oil was distilled to give the free base of **3** (1.48 g, 64.1%): bp 152–154 °C (0.12 mm). The hydrochloride salt of **3** had mp 187–188 °C: CD $[\theta]_{216}$ −21 730° (*c* 0.114, MeOH). Anal. ($C_{15}H_{17}N_2Cl$) C, H, N.

Pharmacology. In vitro drug effects were determined on the isolated, helically cut rabbit aorta, previously denervated by removal of the adventitia.[17] The tissue was suspended in a 10-ml tissue bath (37.5 °C) in Krebs solution under a resting isometric tension of 2 g. The aorta was allowed to equilibrate for a period of 3–3.5 h before drugs were introduced into the bath. Cumulative dose–response curves to agonists were constructed by increasing bath concentrations approximately threefold.[18] To test for antagonist activity, the compound under study was added to the bath for 1 h (to ensure equilibrium) subsequent to construction of a control cumulative dose–response curve to an agonist. The dose–response curve was then repeated in the presence of the antagonist. In all experiments, appropriate corrections were made for changes in sensitivity of the tissue.

References and Notes

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