mp 121.5–123.0°; λ_{max}^{MeOH} 232 mμ (ε 20,440), 263 (15,930), 320 (6360). *Anal.* ($C_{19}H_{16}ClNO_3$) C, H, N, Cl.

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Inhibition of Catecholamine Uptake by Conformationally Restricted Phenethylamine Derivatives

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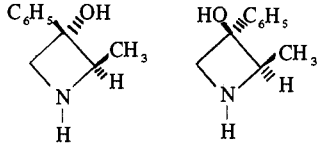
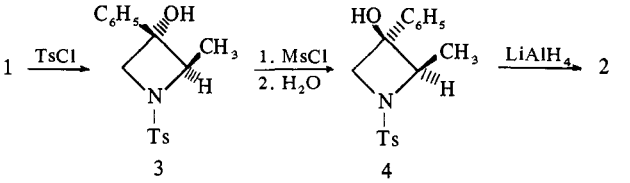
Norepinephrine uptake inhibition is one of the important means by which drugs can affect the adrenergic nervous system. Several studies have appeared on the structural requirements for the inhibition of catecholamine uptake.[1-4] The work on this subject has been reviewed.[5] Previous investigations on the structural requirements of adrenergic drugs have utilized conformationally restricted analogs of phenethanolamine.[6-8]

In an attempt to gain further insight into the stereochemical requirements for the inhibition of catecholamine uptake, we have prepared some azetidine analogs of ephedrine. In this study *trans*-3-phenyl-2-methylazetidin-3-ol (**1**) and *cis*-3-phenyl-2-methylazetidin-3-ol (**2**)† may be considered cyclized ephedrine analogs with a minimum deletion in the number of atoms accompanying the structural change. The azetidines **1** and **2** may be con-



1 **2**

sidered analogous to the threo and erythro configurations of ephedrine, respectively. Hortmann and Robertson[9] have recently reported the synthesis of **1** and an epimeric mixture of **1** and **2**. We would like to report the synthesis of pure **2** utilizing **1** as the starting material. The azetidine **1** was treated with TsCl to give the sulfonamide **3** which in turn was converted to the epimeric sulfonamide **4** by allowing **3** to react first with $MeSO_2Cl$ and then H_2O. The nmr spectrum of **3** showing a shielded methyl doublet at δ 0.87 (J = 6.5 Hz) was consistent with the cis disposition of the methyl group with the phenyl ring, while by comparison the sulfonamide **4** showed a methyl doublet at δ 1.40 (J = 6.5 Hz).[9-11] The sulfonamide **4** was reduced with $LiAlH_4$

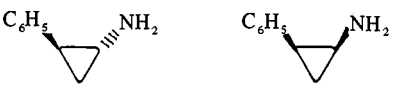


3 **4**

giving the desired **2**[12] and as expected in the nmr spectrum **2** showed a methyl doublet at a lower field δ 1.31 (J = 6.5 Hz) than that observed for **1**, δ 0.74 (J = 6.5 Hz).

Biological Results. The ability of racemic **1** and **2** as well as the desmethylazetidine analog, 3-phenylazetidin-3-ol (**5**),[9] to inhibit (−)-H^3-norephinephrine uptake in rat vas deferens is shown in Table I. Indications are that the stereochemistry of the α-methyl group relative to the phenyl or hydroxyl groups in the azetidine series plays a significant role in the compounds' ability to prevent uptake of (−)-norepinephrine with the relative order of activity being **1** > **2** = **5** in a ratio of 7:1:1.‡

Similarly, *trans*-2-phenylcyclopropylamine (**6**) and *cis*-2-phenylcyclopropylamine (**7**) were investigated for their ability to prevent the uptake of (−)-H^3-norepinephrine in



6 **7**

rat vas deferens as shown in Table I. It is assumed that these compounds are competitive inhibitors of norepinephrine uptake. Using these two conformationally restricted molecules **6** and **7** should provide a better understanding of what the stereochemical relationship should be between the amino and phenyl functions in phenethylamine molecules for the prevention of norepinephrine uptake in the peripheral nervous system. A marked stereospecificity can be seen between the isomers where the trans isomer **6** is greater than 600 times the cis isomer **7** in inhibiting (−)-H^3-norephinephrine uptake in the rat vas deferens. This is quite similar to differences observed by Horn and Snyder[4] for **6** and **7** in blocking norepinephrine uptake in the rat hypothalmus. This seems to indicate that the anticlinical conformation is the preferred conformation for phenethylamine-type drugs in norepinephrine uptake inhibition in both peripheral and central nervous systems.

Experimental Section

Melting points (uncorrected) were determined on a Thomas-Hoover melting point apparatus. Spectral data were obtained using Perkin-Elmer 237 and Varian A-60A spectrometers. Analyses were performed by Clark Microanalytical Laboratory, Urbana, Ill. Analytical results for elements indicated were within ±0.4% of the theoretical values.

Pharmacologic Testing. For the results described in Table I albino rats weighing 305–395 g were killed and both vasa deferentia were isolated. Tissues were transferred to an oxygenated 5-ml Kreb's solution at 37.5°. The tissue monoamine oxidase which degrades norepinephrine was inhibited by exposing the tissue to 10^{-4} M iproniazid for 30 min. The iproniazid-inhibited tissues were transferred to two beakers each containing 5 ml of the Kreb's solution. Thus, one tissue served as a control and the contralateral tissue served as experimental. Both tissues were incubated with (−)-H^3-

†Cis and trans refer to the relationship between the C-2 CH_3 and the C-3 OH; thus, **1** has CH_3 trans to OH and **2** has CH_3 cis to OH. All materials are racemic although only a single isomer is drawn.

‡As compared to the effects produced by **2**, the contraction of the isolated vas deferens to (−)-norepinephrine (10^{-6} M) was potentiated more by 10^{-5} M (3-min incubation) of **1**.

Table 1.[12] Inhibition of Uptake of (−)-H^3-Norepinephrine (10 ng/ml, 28.5 nCi/ml, 30-min Incubation) by the Drugs in the Rat Vas Deferens

Drug	Concn, *M*	Uptake of (−)-H^3-NE with SEM, cpm/tissue: Control	Uptake of (−)-H^3-NE with SEM, cpm/tissue: With inhibitor[b]	% of control uptake with SEM	Approx rel activity[c]
Control[a]		3332 ± 150			
1	7×10^{-5}		1171 ± 129	35 ± 3	
Control[a]		3118 ± 155			
2	1×10^{-4}		2158 ± 93	70 ± 4	
Control[a]		3167 ± 441			
2	1×10^{-3}		633 ± 26	21 ± 2	1 > 2 (7:1)
Control[a]		3660 ± 437			
5	5×10^{-4}		1136 ± 105	31 ± 1	1 > 5 (7:1)
Control[a]		3577 ± 333			
6	1×10^{-5}		1347 ± 14	38 ± 3	
Control[a]		3900 ± 321			
6	1×10^{-4}		538 ± 30	14 ± 3	
Control[a]		3500 ± 177			
7	3×10^{-4}		2539 ± 327	72 ± 6	6 > 7 (662:1)

[a]Contralateral tissue was used as control. [b]Incubation time, 15 min. [c]Determined from the graphic plot.

norephinephrine (28.5 nCi/ml, 10 ng/ml for 30 min) except the experimental tissue was incubated for 15 min with the inhibitor of the neuronal uptake prior to the addition of (−)-H^3-norephinephrine. The extraneuronal radioactivity was cleared by washing the tissues for 5 min in two volumes of the Kreb's solution. The tissue was blotted and weighed and the radioactivity was extracted with 2 ml of perchloric acid (0.4 *N*). The supernatum after centrifugation was counted in 13 ml of Aquasol. The vials were counted in a liquid scintillation spectrophotometer.

The tests were repeated three times, and data are reported as mean with the SEM. Since the weights of the contralateral tissues do not deviate more than 4 mg, the uptake of (−)-H^3-norepinephrine is expressed per tissue. It is assumed that liberation of endogenous norepinephrine by these compounds does not affect the relative uptake of (−)-H^3-norepinephrine. Ideally, ID_{50} should be used to determine the relative catecholamine inhibitory effects of drugs. However, the quantity of the material at our disposal was too small to do so. The details of the quantification will be examined in the future. The relative potency was obtained by semilog plot.

trans-3-Phenyl-2-methylazetidin-3-ol (1). The method described by Hortmann and Robertson[9] was employed in preparing 1. The HCl salt of 1 was prepared and recrystallized from $CHCl_3$, mp 179–180°. *Anal.* ($C_{10}H_{14}NOCl$) C, H, N.

trans-3-Phenyl-2-methyl-1-*p*-toluenesulfonamidoazetidin-3-ol (3). To a stirred solution of 2.3 g (0.012 mol) of the HCl salt of 1 in 25 ml of pyridine was added 2.6 g (0.013 mol) of TsCl. The resulting mixture was allowed to stand 48 hr at room temperature. The yellow mixture was then poured into 40 ml of ice H_2O and stirred for 30 min. The resulting white solid was removed by filtration. The white solid was then taken up in $CHCl_3$, dried (Na_2SO_4), and evaporated to give a white solid (3.5 g, 92%). A portion was crystallized from C_6H_6 giving a white solid: mp 160°; nmr ($CDCl_3$) δ 0.87 (d, 3, J = 6.5 Hz), 2.46 (s, 3), 2.63 (s, 1), 3.5–4.3 (m, 3), 7.1–7.9 (m, 9). *Anal.* ($C_{17}H_{19}NO_3S$) C, H, N.

cis-3-Phenyl-2-methyl-1-*p*-toluenesulfonamidoazetidin-3-ol (4). A mixture of 2 g (6.3 mmol) of sulfonamide 3, 2.06 g of MsCl, and 40 ml of pyridine was maintained at 5° for 72 hr. The mixture was then poured into ice H_2O and stirred overnight. The resulting white precipitate was removed and then taken up in $CHCl_3$. The $CHCl_3$ solution was dried (Na_2SO_4) and evaporated to give 1.8 g of an epimeric mixture of 3 and 4 in a ratio of 3:7 using nmr. The mixture was taken up in 30 ml of C_6H_6 and allowed to sit overnight at room temperature. Clear plate-like crystals of pure 4 (980 mg, 49%) were isolated: mp 138–139°; nmr ($CDCl_3$) δ 1.40 (d, 3, J = 6.5 Hz), 2.45 (s, 3), 3.28 (s, 1), 3.91 (s, 2), 4.16 (q, 1, J = 6.5 Hz), 6.8–7.5 (m, 7), 7.65–7.9 (m, 2). *Anal.* ($H_{17}H_{19}NO_3S$) C, H, N.

cis-3-Phenyl-2-methylazetidin-3-ol (2). Compound 4 (500 mg, 1.58 mmol) was placed in 10 ml of THF and to this was added 500 mg (14 mmol) of $LiAlH_4$ and the mixture was stirred 18 hr at room temperature. The reaction mixture was then carefully decomposed by adding wet ether, followed by water. The solid material was removed by filtration and washed with THF. The THF solution was then dried (Na_2SO_4) and evaporated *in vacuo* to give a white solid. The solid was taken up in ether and 116 mg (45%) of pure 2 was isolated: mp 133°; nmr ($CDCl_3$) δ 1.31 (d, 2, J = 6.5 Hz), 3.54 (d, 1, J = 9 Hz), 3.68 (s, 2, OH and NH), 4.00 (d, 1, J = 9 Hz), 4.20 (q, 1, J = 6.5 Hz), 7.1–7.6 (m, 5). *Anal.* ($C_{10}H_{13}NO$) C, H, N.

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Some Anticonvulsant and Cardiovascular Effects of Substituted Thiazolidones†

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Diverse biological properties exhibited by substituted thiazolidones include hypnotic[1] and local anaesthetic[2] activities. The effectiveness of 2-(4-chlorophenyl)-3-methyl-4-thiazolidone and 2-(2-furyl)-3-methyl-4-thiazolidone to afford protection against pentylenetetrazol-induced seizures[3] has also been reported. These observations prompted us to synthesize 2-substituted-imino-3-substituted-5-carboxymethyl-4-thiazolidones and to evaluate their anticonvulsant activity, their effects on resting blood pressure, and their ability to selectively inhibit NAD-dependent oxidations.[4]

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