3324-71-8; MeOCONCS, 35266-49-0; PrNH₂, 107-10-8; *i*-PrNH₂, 75-31-0; BuNH₂, 109-73-9; *t*-BuNH₂, 75-64-9; H₃C(CH₂)₄NH₂, 110-58-7; H₂C=CHCH₂NH₂, 107-11-9; PhCH₂NH₂, 100-46-9; *c*-C₅H₉NH₂, 1003-03-8; HOCH₂CH₂NH₂, 141-43-5; HO(CH₂)₃NH₂, 156-87-6; Me₂N(CH₂)₃NH₂, 109-55-7; H₂NCN, 420-04-2; PhNH₂, 62-53-3; *c*-C₄H₇NH₂, 2516-34-9; MeO(CH₂)₂NH₂, 109-85-3; MeO-(CH₂)₃NH₂, 5332-73-0; EtO(CH₂)₂NH₂, 110-76-9; Ph(CH₂)₂NH₂, 64-04-0; H₃CCH(OH)CH₂NHMe, 16667-45-1; MeS(CH₂)₂NH₂, 18542-42-2; AcNH(CH₂)₂NH₂, 1001-53-2; MeONH₂, 67-62-9; MeNH₂, 74-89-5; H₂N(CH₂)₂NH₂, 811-93-8; MeNH(CH₂)₂NH₂, 109-81-9; H₂N(CH₃)₂CH₂NH₂, 109-76-2; H₂NCH₂C(OMe)₂, 22483-09-6; guanidine carbonate, 100224-74-6; [5-(2-iodophenyl)-1,3,4-thiadiazol-2-yl]cyanamide, 113113-50-1; [5-(2-methyl-4-

fluorophenyl-1,3,4-thiadiazol-2-yl]cyanamide, 113113-52-3; [5-(3,4-dimethoxyphenyl)-1,3,4-thiadiazol-2-yl]cyanamide, 113113-53-4; potassium[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]dithiocarbamic acid, 113113-24-9; 1-*n*-butyl-3[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]thiourea, 113113-25-0; S-methyl[5-(2-iodophenyl)-1,3,4-thiadiazol-2-yl]dithiocarbamate, 113113-44-3; Smethyl[5-(2,4-dimethylphenyl)-1,3,4-thiadiazol-2-yl]dithiocarbamate, 113113-45-4; [5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]dithiocarbamate, 113113-46-5; 2-(methylphenyl)-1,3,4-thiadiazol-2-yl]dithiocarbamate, 113113-46-5; 2-(methylphenyl)-1,3,4-thiadiazol-2-yl] ghenyl)-1,3,4-thiadiazole, 113113-47-6; 1-(2-dimethoxyethyl)-2-[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]guanidine, 113113-48-7; 1-(formylmethyl)-2-[5-(2-methyphenyl)-1,3,4-thiadiazol-2-yl] guanidine, 113113-49-8; pyrrolidine, 123-75-1; morpholine, 110-91-8; *N*-methylpiperazine, 109-01-3; 2-(aminomethyl)tetrahydrofuran, 4795-29-3.

Homoallylic Amines Related to Zimeldine. A Comparative Study on Neuronal Serotonin and Norepinephrine Reuptake Based on Conformational Analysis

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A number of tertiary and secondary homoallylic amines, i.e. (Z)- and (E)-4-(4-bromophenyl)-4-(3-pyridyl)-3-buten-1-ylamines, were synthesized in diastereomerically pure forms. The compounds were evaluated as neuronal norepinephrine (NE) and serotonin (5-HT) uptake inhibitors under in vitro and ex vivo conditions and compared with the tricyclics amitriptyline and nortriptyline having homoallylic side chains and with the corresponding diastereomers in the zimeldine series having allylic side chains. The Z isomers of the new homoallylic derivatives (3Z, 4Z) were specific 5-HT uptake inhibitors in analogy with the corresponding allylic derivatives zimeldine (1Z)and norzimeldine (2Z). Likewise, the selectivity profile of the homoallylic (3E, 4E) and the allylic (1E, 2E) derivatives was comparable. In general, the homoallylic compounds were less potent inhibitors than their allylic counterparts. The similarities and discrepancies were evaluated in terms of conformational preferences determined by CAMSEQ molecular mechanics calculations. Homonorzimeldine (4Z) can accommodate energetically favored, but less populated, conformations having amino nitrogen atom to aromatic ring center distances comparable to those in norzimeldine. These facts correlate to retained 5-HT selectivity but diminished potency of 4Z compared to 2Z.

Numerous tricyclic agents have been developed since the discovery of imipramine as a useful agent in the treatment of depression.¹ Still, their mode of action is not beyond dispute, even if the most widely held theory is an initial blockade of the neuronal reuptake of monoamine transmitters by the tricyclics.^{2,3} The controversy over their mode of action is partly due to the wide spectrum of pharmacological effects associated with the tricyclics.^{1b,3} This led to the search for more selective agents, and the focus was directed especially toward selective 5-hydroxytryptamine (5-HT) uptake inhibitors,^{4,5} an interest based on the possible involvement of 5-HT in the control of the mood component of the syndrome.⁶ Among these compounds, zimeldine (1Z, Chart I) proved to be a clinically effective antidepressant,^{7,5} which lends good support for the 5-HT hypothesis for antidepressant action. The drug was withdrawn from the market due to the unexpected occurrence of Guillain-Barré syndrome during treatment with zimeldine.8

Zimeldine is almost devoid of action on most neurotransmitter receptors, including α_1 -, α_2 -, and β -adrenergic, serotonergic, histaminergic, and muscarinic.⁹ In addition, it has a stereoselective action with respect to uptake inhibition.^{4g,10} Thus, the Z isomers 1Z and 2Z are selective neuronal 5-HT uptake inhibitors, whereas in the E series, Chart I. Structures of Allylic and Homoallylic Amines Investigated (1Z, zimeldine; 2Z, norzimeldine; 5, amitriptyline; and 6, nortriptyline)



especially the secondary amine 2E is more active as a norepinephrine (NE) uptake inhibitor (Chart I). It is

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Table I. Influence of the Halogenating Reagent in Homoallylic Rearrangement of 8 and Allylic Rearrangement of 13 on the Stereochemistry in the Product^a

		Br	N OH 13 ^b			
$reagent^c$	conversion to 9 or 10, %	Z, %	conversion to 1, %	Z, %		
PCl ₅	91	66	100	86		
PCl ₃	88	70	100	71		
$SOCl_2$	33	67	94	60		
HCl	no^d		no^d			
$HCl/ZnCl_2$	99	61	100	50		
PBr_5	98	75				
PBr_3	95	74				
HBr/HOAc	74^{e}	78				

^a The alcohol 8 or 13 (0.2 mmol) was treated with excess halide in 5 mL of CH_2Cl_2 during 3 h at room temperature. In the case of 13, the allylic chloride formed was reacted with excess HNMe₂ and analyzed as amine 1. In the case of 8, the solution of halide 9 or 10 was washed with 1 M Na₂CO₃ prior to analysis. The reactions were analyzed on capillary GLC equipped with an electronic integrator, assuming identical response factors. ^b Data taken from ref 10. ^cThree equivalents of halide was used with 8 and 1.5–2 equiv of halide with 13. ^d No conversion with anhydrous HCl. ^eTenhour reaction time. 8 13^b

important to note that the selectivity is retained for the principal metabolite of zimeldine,¹¹ the secondary amine norzimeldine (2Z), since this is in contrast with the general behavior of tricyclic tertiary and secondary amines.^{6b,12} Furthermore, in tricyclic antidepressants, the aromatic

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rings are normally separated by three carbon atoms from the basic nitrogen. For example, amitriptyline (5), nortriptyline (6), doxepin, and melitracene have homoallylic side chains,¹³ whereas zimeldine (1Z) and 2Z have allylic side chains (Chart I). In light of the many promising features of zimeldine, it was of interest to see whether a homoallylic side chain could be applied in this case as well. It has been reported that a series of 3,3-diphenylallylamines antagonized reserpine-induced hypothermia in mice, indicating inhibition of the norepinephrine reuptake,4c but the corresponding tertiary 4,4-diphenylhomoallylamine was inactive.¹⁴ However, the possibility remains that this compound selectively inhibits the 5-HT uptake. Apart from this somewhat discouraging result, similar studies seem to be lacking.¹³ In our case, we have the added challenge of preserving the 5-HT selectivity. This makes it necessary to prepare the compounds in diastereomerically pure and established forms. The present study describes the synthesis and stereochemical assignments of 3Z, 3E, 4Z, and 4E (Chart I). The compounds were evaluated as uptake inhibitors under in vitro and ex vivo conditions and compared with the allylic counterparts as well as the tricyclics 5 and 6. Conformational analysis of three selected compounds (2Z, 2E, and4Z), all being fairly specific neuronal uptake inhibitors. was made in order to see if pharmacological activity and selectivity correlate with conformational preference.

Chemistry

Zimeldine (1Z) and norzimeldine (2Z) have been obtained by various synthetic routes such as the Wittig reaction, ^{15a} dehydration, ^{15a} stereoconservative reductive amination, ^{15b} palladium-catalyzed amination, ^{15c} and stereoselective allylic rearrangement. ^{15d,10} The latter method offered an efficient way of obtaining a high yield of the desired Z isomer from the easily obtained allylic alcohol 13 (cf. Table I). We decided to adopt a similar approach in the synthesis of the homoallylic amine 3, in order to try to optimize formation of the Z isomer. For comparison, see the synthesis of amitriptyline by homoallylic rearrangement.¹⁶

Accordingly, the ketone 7 was reacted with cyclopropylmagnesium bromide to give the cyclopropylcarbinol 8 in 80% yield. The homoallylic rearrangement of 8 was effected by various reagents as shown in Table I. In



contrast to the allylic rearrangement of 13, no marked

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Table II.	Configurational	Assignments o	f Homoallylic	: Amines 3 an	d4 by N	Means of	EUV (0.	.1 M HCl) a	and ¹ H N	IMR ((CDCl ₃)
Spectrosco	ору										

no.	UV	7		¹ H NMR, ppm		_
	λ_{max} , nm	€ _{max}	2-ру	6-ру	vinyl	
1 <i>Z</i> ^a	250	19700	8.46	8.60	6.30	
$1E^a$	219	21 900	8.53	8.50	6.27	
3 <i>Z</i>	249	20600	8.58	8.69	6.28	
3 E	225	20600	8.60	8.56	6.24	
4Z	250	23 500	8.60	8.68	6.28	
4E	224	21700	8.62	.8.58	6.24	

^aStereochemistry unambiguosly determined by means of X-ray single-crystal analysis $(1Z)^{18}$ and lanthanide-induced shifts in ¹H NMR $(1Z, 1E)^{17}$ analysis.

Table III. Inhibition of the Accumulation of (-)-[³H]Norepinephrine (NE) and [¹⁴C]-5-Hydroxytryptamine (5-HT) in Synaptosomes from the Rat Brain Cortex and in Slices from the Middle Part of the Mouse Brain^a

			synaptosomes, rat: in vitro IC_{50} , μM		slices, mouse: in vitro IC ₅₀ , μ M			slices, mouse: ex vivo ED_{50} , $\mu mol/kg$, ip		
compound	amine	side chain	NE	5-HT	ratio ^b	NE	5-HT	ratio ^b	NE	5-HT
zimeldine $(1Z)$	tert	allyl	3.2	0.10	32	24 ^d	1.7^{d}	14	>98 (26%) ^{c,d}	49 ^d
norzimeldine $(2Z)$	sec	allyl	0.24	0.038	6.3	1.5^{d}	0.10^{d}	15	>102 (38%) ^d	19 ^d
3 <i>Z</i>	tert	homoallyl	22.5	0.50	45	>24 (20%)	0.90	>27	>95 (15%)	95 (57%)
4 <i>Z</i>	sec	homoallyl	6.6	0.24	28	>25 (20%)	0.50	>50	>98 (1%)	>98 (35%)
1 <i>E</i>	tert	allyl	0.15	0.22	0.68	6.1^d	6.1^{d}	1.0	25^d	>98 (36%) ^d
2E	sec	allyl	0.0046	0.080	0.058	0.8^d	2.5^{d}	0.32	25 ^d	102 ^d
3 <i>E</i>	tert	homoallyl	1.4	2.6	0.54	7.8	7.1	1.1	95 (18%)	>95 (11%)
4 <i>E</i>	sec	homoallyl	1.0	1.4	0.71	0.25	0.12	2.1	98 (32%)	>98 (11%)
amitriptyline (5)	tert	homoallyl	0.061	0.32	0.19	5.4	2.9	1.9	114	>114 (43%)
nortriptyline (6)	sec	homoallyl	0.007	2.0	0.0035	0.5	6.7	0.075	67	>133 (31%)

^aSee the Experimental Section for details. ^bSelectivity expressed as ratio between NE and 5-HT uptake inhibition. ^cThe values in parentheses indicate the inhibition at the highest dose level in percent. ^dData taken from ref 10.

difference in the stereochemical outcome in the formation of 10 was observed for the different chlorination reagents (PCl₅, PCl₃, SOCl₂, HCl/ZnCl₂), i.e., about 67% of the Z isomer 10 was produced. As can be seen, the bromination reagents (PBr₅, PBr₃, HBr) also gave similar stereochemical results in the homoallylic rearrangement leading to 9, but the stereoselectivity (ca. 75% Z) was slightly better than with the chlorides. For preparative purposes, phosphorus tribromide was the reagent chosen. The homoallylic bromide 9 was isolated in 99% yield with the Z/E isomeric ratio of 74:26 as found in the small-scale experiment. The stereochemical assignment was based on the chemical shifts of the vinyl protons of the two isomers of 9 [i.e., δ 6.24 (minor, E) and 6.28 (major, Z)] in comparison to 3 (cf. Table II).

The crude bromide 9 was reacted with dimethylamine in THF to give the isomeric amines 3Z and 3E in yields (GLC) of 39% and 14%, respectively. In addition, a considerable amount of the isomeric mixture of the elimination product 11 was isolated (46%). Procedures to separate the isomers of 3 (as hydrochloride or oxalate)¹⁰ or the precursor 9 (as picrate)^{15b} by fractional crystallizations failed completely, in contrast to the easy separated in the allylic case. Therefore, the amines 3 were separated by repeated preparative HPLC.

Analogously, 9 was reacted with methylamine in THF to produce the expected mixture of 4Z (42%), 4E (20%), and diene 11. In addition, another aliphatic amine was isolated as a side product. The amine components were separated by preparative HPLC and radial TLC to give pure 4Z and 4E and the side product, which surprisingly proved to be an isomeric mixture of the primary homoallylic amine 12. Possibly, ammonia present as an impurity in the methylamine reacted considerably faster with the bromide 9.

The configurations of the tertiary amines 3E and 3Zwere established by analysis of the europium-induced shifts in ¹H NMR spectrum of the amine mixture (see the Experimental Section).^{10,15c,17} Besides, the stereostructure of the isolated homoallylic amines 3 and 4 was related to the known allylic amines 1 by means of UV or ¹H NMR spectroscopy as shown in Table II.

Inhibition of NE and 5-HT Accumulation

Methods. The accumulation of ³H-labeled norepinephrine (NE) and ¹⁴C-labeled serotonin (5-HT) was determined in three different assays according to previously described procedures, i.e., in synaptosomes from rat brain cortex and in slices from the middle part of the mouse brain under in vitro as well as ex vivo conditions.^{4c,4g,10,19} The inhibition of the accumulation was determined as percent of control, and the IC₅₀ and ED₅₀ values were estimated from semilogarithmic plots (Table III). The ratios of the NE/5-HT uptake inhibition for the in vitro experiments are included for clarity.

As a general trend it should be noted that the IC_{50} values obtained in the rat synaptosomes are lower than the corresponding values in the mouse slices, indicating a more facile distribution of the compounds to the synaptic cleft. However, the ratios of the NE/5-HT uptake inhibitions are of the same magnitude in the two tests for the different compounds investigated.

Structure-Activity Relationships. As mentioned earlier, zimeldine (1Z) and the secondary amine 2Z, both exhibit large NE/5-HT ratios, although 2Z is considerably more potent than 1Z.^{4g,10} This is in contrast with the situation for most tricyclics, even if the present example with the homoallylic amines 5 and 6 is not as evident as others, e.g., imipramine vs desipramine.¹⁰ However, it can be seen that the tertiary amine amitriptyline (5) is more potent as a 5-HT uptake inhibitor than the secondary amine 6, and the reverse applies for the NE uptake in-

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Figure 1. Torsion angles for the allylic and homoallylic amines subjected to molecular mechanics calculations: $\tau_1 = C_1 - C_6 - C_7 - C_{14}$, $\tau_2 = C_9 - C_8 - C_7 - C_{14}$, $\tau_3 = C_7 - C_{14} - C_{15} - C_{16}(N_{16})$, $\tau_4 = C_{14} - C_{15} - C_{16}(N_{16}) - N_{17}(C_{17})$, $\tau_5 = C_{15} - C_{16} - N_{17} - C_{18}$ (Table IV).

hibition. With these discrepancies between 1Z/2Z and 5/6 in mind, it is interesting to note that the homoallylic amines 3Z and 4Z show the same pattern as 1Z and 2Z, i.e., 5-HT selectivity for both the tertiary and secondary amine.

The tertiary amine 1E exhibits the same activity for NE and 5-HT, and this observation holds for the homoallylic counterpart 3E. The most notable difference between the allylic and homoallylic derivatives is found between 2E and 4E, since the secondary amine 4E is only equipotent with the corresponding tertiary amine 3E, whereas the allylic derivative 2E is more active than 1E.

Conformational Analysis

Conformational analyses were carried out on selected members of the zimeldine series studied to find out if pharmacological activity could be correlated with conformational preference. The three secondary amines, norzimeldine (2Z), the E isomer (2E), and homonorzimeldine (4Z) were examined. All of these compounds exhibit relatively high neuronal selectivity, i.e., 2Z and 4Z for 5-HT and 2E for NE uptake inhibition.

Methods. The CAMSEQ²⁰ molecular mechanics software system was used. CAMSEQ has previously given satisfactory results in calculations of low-energy conformations of phenethylamine systems and other neuronal uptake inhibitors.^{21,22} The method computes total energy as a sum of steric (dispersion), electrostatic, torsional, H bond, and solvation terms. Pairwise nonbonded interaction energies are calculated by using sets of Lennard-Jones 6-12 potential functions. Pairwise electrostatic interaction energies are approximated by the general Coulomb's law type of function, $U = kQ_1 \cdot Q_2/r$, where k is the units constant and Q_1 and Q_2 are the partial charges on the atoms at distance apart r. The σ -charge contribution is calculated by using a modified Del Rey method as reported by Poland and Scheraga, and the π -charge contribution is calculated in analogy with their suggestions.²³

The starting coordinates were taken from the X-ray data on zimeldine.¹⁸ The calculations were carried out in stages. First, the preferred torsion angles were established for the diaryl segments (τ_1 and τ_2 rotations, Figure 1), and then the side-chain orientation was examined (torsion angles τ_3 , τ_4 , and τ_5). The results of these two procedures were then combined, and the likely favorable conformations for

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Figure 2. Molecular graphics $(SYBYL)^{24}$ overlay drawing of norzimeldine (2Z), light lines) in conformation 3 and (E)-norzimeldine (2E, heavy lines) in conformation 4. The aryl ring centers and aliphatic nitrogens were subjected to a least-squares fit (dashed lines).



Figure 3. Molecular graphics $(SYBYL)^{24}$ overlay drawing of norzimeldine (2Z), heavy lines) in conformation 1 and homonorzimeldine (4Z), light lines) in conformation 3. The aryl ring centers and aliphatic nitrogens were subjected to a least-squares fit (dashed lines).

the molecule as a whole were investigated over restricted regions of space (four variables for the allylamines 2Z and 2E, five for the homoallylamine 4Z). Both neutral and monoprotonated species were examined, and the low-energy conformations found were similar.

Results. Table IV lists low-energy conformations and important intramolecular distances for the monoprotonated species. Compared to homonorzimelidine (4Z), both norzimelidine (2Z) and the E isomer (2E) are relatively stable geometrically across the observed favored conformations from the point of view of amino nitrogen atom to aromatic ring center distances. These show relatively small deviations from average values, reflecting the restrictive influence of the double bond in the allylic amine side chain. In particular, the amino nitrogen atom to phenyl ring center distance in norzimelidine (2Z) shows a maximum deviation of only 3.4% from its average value of 5.79 Å, while the corresponding distance measurements in the observed favored conformations of the homologue 4Z show a deviation of about 31%. Generally speaking, norzimelidine (2Z) and the E isomer (2E) are similar in basic geometric shape [see, for example, the SYBYL²⁴ overlay drawing of 2Z (3) and 2E (4), Figure 2]. The reversal of the pyridine and phenyl ring positions in going from one to the other reverses the amino nitrogen atom to aryl ring center distances.

For both the allylamines 2Z and 2E there are observed two particularly favorable ring-ring orientations with the following τ_1 and τ_2 torsion angles: (a) τ_1/τ_2 (or τ_2/τ_1) \approx

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Table IV. Low-Energy Minima Calculated by the CAMSEQ Molecular Mechanics Method (Pertinent Intraatomic Distances Used in Conformational Comparisons Are Indicated)

									distances, A	
			torsic	sion angles, ^a deg			energy above global min,	phenyl to pyridyl	phenyl center to	pyridyl center to
compound		$\underline{\tau_1}$	τ_2	$ au_3$	$ au_4$	$ au_5$	kcai moi ·	centers	amine	amine
norzimelidine, 2Z	(1)	140	170	280	60		0.0	4.88	5.94	4.20
	(2)	230	0	80	300		0.8	4.86	5.82	4.18
	(3)	60	0	40	40		0.8	4.89	5.70	3.33
	(4)	240	180	40	40		1.2	4.89	5.69	3.32
,							average:	4.88	5.79	3.76
				maxin	num dev	viation	from average:	± 0.03	±0.2	±0.4
(E)-norzimelidine. $2E$	(1)	170	120	280	50		0.0	4.91	3.95	5.92
()	(2)	180	50	40	40		0.2	4.86	3.30	5.78
	(3)	180	60	80	300		0.8	4.84	4.16	5.89
	(4)	10	220	40	40		1.4	4.97	3.25	5.76
							average:	4.90	3.67	5.84
				maxin	num dev	viation	from average:	±0.1	±0.5	± 0.1
homonorzimelidine. $4Z$	(1)	230	10	30	80	300	0.0	4.90	3.58	6.08
	(2)	250	0	90	300	290	1.6	4.89	3.13	5.76
	(3)	130	180	320	320	310	2.7	4.93	5.34	3.12
	(4)	140	170	330	170	280	2.7	4.94	5.66	5.67
	(5)	130	180	270	70	270	3.0	4.93	5.51	3.60
	(6)	150	160	90	20	270	3.5	4.94	3.70	6.14
							average:	4.92	4.49	5.06
				maxin	num dev	viation	from average:	±0.03	±1.4	±1.9

^a The torsion angles are indicated in Figure 1.

60° (or 60° + 180°)/0° (or 0° + 180°) and, (b) τ_1/τ_2 (or $\tau_2/\tau_1) \approx 120^\circ - 140^\circ/170^\circ - 180^\circ$. As indicated in Table IV, chain conformations also are similar in both isomers.

Homonorzimelidine (4Z) retains the two ring-ring geometry preferences (τ_1/τ_2 torsion angle positions) of the allylamines. On the other hand, 4Z exhibits, as might be expected, greater variation in chain orientation and thus a relatively wide spectrum of amine nitrogen atom to ring center distances (Table IV). In fact, the increased length of the chain permits the presentation of energetically favored conformations in which amino nitrogen atom to aromatic ring center distances closely approximate the corresponding distances in the allylamines. There is also a conformation [4Z (4)] in which the amino nitrogen atom is equally distanced from the two aromatic centers (about 5.7 Å).

The SYBYL²⁴ drawing in Figure 3 shows an overlay of homonorzimelidine [4Z (3)] with norzimelidine [2Z (1)]. Amino nitrogen atoms and aromatic centers superimpose fairly well, showing that the basic geometric requirements for 5-HT blocking activity, as dictated by the norzimelidine geometry, can also be accommodated in a favored conformation of 4Z, in spite of the increased chain length. However, the stability across the observed preferred conformations of the amino nitrogen atom to phenyl ring center distances of norzimelidine is not present in the observed favored conformations of the homologue 4Z.

Conclusions

Although the selectivity for inhibition of uptake of 5-HT compared to NE is retained in homonorzimeldine (4Z), the potency in synaptosomes (for both NE and 5-HT uptake inhibition) of 4Z is 1 order of magnitude less than for 2Z. The added flexibility in the side chain of 4Z allows it to assume a variety of low-energy conformations, more than in 2Z. While it is possible for 4Z to assume a conformation placing the key pharmacophoric groups in a similar arrangement in space as for 2Z (Figure 3), the decrease in potency may be related to an effective dilution of the concentration of the active conformer at the uptake sites. This would account for a lowered potency, yet a

retained selectivity, compared to 2Z.

It might be concluded that the allylic chain length in 2Z and 2E is particularly adapted to giving optimal amino nitrogen atom to aromatic center distances. The striking difference in selectivity for NE and 5-HT uptake inhibition between the E and Z isomers is likely to arise from the influence of the *p*-bromo substituent rather than conformational effects (see overlay in Figure 2). This is further supported by the substituent influence on the activity and selectivity in this series of compounds.¹⁰

Experimental Section

Chemistry. Melting points were determined on a Mettler FP 61 apparatus and are uncorrected. ¹H NMR spectra were recorded on a Varian EM 360 A with Me₄Si as internal standard. Mass spectra (EI, 70 eV) were recorded on an LKB 9000 instrument. GLCs were run on an SE 30 capillary column, and the amounts were determined by a Hewlett-Packard 3390 A integrator. Preparative HPLC was conducted on a Waters LC 500 apparatus, and preparative, centrifugally accelerated, radial TLC was conducted on a Chromatotron from Harrison Research. Elemental analyses, performed by Analytische Laboratorium, Elbach, West Germany, were within $\pm 0.4\%$ of the theoretical values unless otherwise noted.

1-(4-Bromophenyl)-1-cyclopropyl-1-(3-pyridyl)carbinol (8). A solution of cyclopropyl bromide (15.1 g, 0.125 mol) in 40 mL of dry tetrahydrofuran (THF) was added dropwise to magnesium turnings (3.2 g, 0.13 mol) in 10 mL of THF at reflux over 50 min under N_2 . After being stirred for another 30 min at 70 °C, the solution was diluted with 50 mL of THF to prevent precipitation of the Grignard reagent. The hot solution was transferred via syringe to a dropping funnel and added to a solution of (4bromobenzoyl)-3-pyridine (7, 26.2 g, 0.10 mol) in 90 mL of THF at ice-bath temperature. The mixture was stirred at ambient temperature for 1 h and then treated with a solution of NH₄Cl (10.7 g, 0.2 mol) in 50 mL of water at ice-bath temperature. The mixture was filtered and washed with ether. The organic layer was evaporated, and the residue was taken up in ether and washed with water and brine. Drying (MgSO₄) and evaporation gave 32.2 g crude material (ca. 93% purity by GLC) of which 20 g was subjected to flash chromatography on SiO_2 with $i-\bar{P}r_2O/$ $MeOH/NH_3$ (100:10:1) to give 15.1 g (80%, yield calculated on chromatographed material) of pure alcohol 8. An analytical sample was recrystallized from ether, mp 100-102 °C: ¹H NMR

 $\begin{array}{l} ({\rm CDCl}_3) \ \delta \ 0.55 \ ({\rm m}, \, 4, \, {\rm CH}_2{\rm CH}_2), \, 1.49 \ ({\rm m}, \, 1, \, {\rm CH}), \, 4.35 \ ({\rm s}, \, 1, \, {\rm OH}), \\ 7.1-7.7 \ ({\rm m}+{\rm AA'BB'}, \, 5, \, {\rm aromatic}), \, 7.82 \ ({\rm dt}, \, 1, \, 4\mbox{-}{\rm pyridyl}), \, 8.34 \ ({\rm dd}, \, 1, \, 6\mbox{-}{\rm pyridyl}), \, 8.53 \ ({\rm d}, \, 1, \, 2\mbox{-}{\rm pyridyl}); \, {\rm MS}, \, m/z \ ({\rm relative intensity}) \\ 305/303 \ ({\rm M}, \, 1.6/1.6), \, 277/275 \ ({\rm M}-{\rm C}_2{\rm H}_4, \, 94/100), \, 264/262 \ ({\rm M}-{\rm C}_3{\rm H}_5, \, 25/25), \, 196 \ (9), \, 185/183 \ (23/23), \, 157/155 \ (12/13), \, 106 \ (91). \ {\rm Anal.} \ ({\rm C}_{15}{\rm H}_{14}{\rm BrNO}) \ {\rm C}, \, {\rm H}, \, {\rm N}, \, {\rm Br}, \, {\rm O}. \end{array}$

4-Bromo-1-(4-bromophenyl)-1-(3-pyridyl)-1-butene (9). A solution of cyclopropylcarbinol 8 (5.25 g, 0.17 mol) in 150 mL of CH₂Cl₂ was cooled in an ice bath, and PBr₃ (2.35 mL, 0.25 mol) was injected. The cooling bath was removed after 0.5 h. GLC showed complete conversion. The mixture was cooled and quenched with 100 mL of ice and 100 mL of 1 N Na₂CO₃. After dilution with water, the mixture was extracted with CH₂Cl₂ twice. The organic layer was washed with water and brine, dried (Mgs SO₄), and evaporated to give 6.20 g (99%) of an oil. GLC showed the Z/E isomeric ratio of 74:26: ¹H NMR (CDCl₃) δ 2.72 (app q, 2, CH₂), 3.50 (t, 2, CH₂Br), 6.24 (t, minor E, CH), 6.28 (t, major Z, CH), 7.1–7.8 (m, 6), 8.4–8.7 (m, 2, 2,6-pyridyl). The configurational assignment was made by lanthanide-induced shifts in ¹H NMR of the amination product 3 (cf. chemical shifts of vinyl triplets in 9 and 3).

4-(4-Bromophenyl)-N,N-dimethyl-4-(3-pyridyl)-3-buten-1-ylamine (3). The bromide 9 (6.1 g, 0.017 mol) was dissolved in 30 mL of THF, and 20 mL of a solution of dimethylamine in THF (1:1) was added. After being stirred overnight, the solvent was evaporated, and the residue was taken up in ether and washed with aqueous NaHCO₃. GLC (capillary column SE 30, 240 °C) showed two components (11) with retention times 2.53 and 2.57 min (total 44%) and two components with retention times 3.93 min (14% 3E) and 4.10 min (39% 3Z), i.e., a retained isomeric ratio of 74:26. The ethereal layer was extracted three times with aqueous acetic acid. The ethereal layer was evaporated, and the residue was taken up in CH₂Cl₂ and washed twice with 2 M NaOH to remove acetic acid. Drying (MgSO₄) and evaporation gave 2.18 g (46%) of isomeric butadienes 11: MS (EI, 70 eV), m/z (relative intensity) 287/285 (M, 17/17), 206 (M – Br, 100).

The aqueous acetic acid phase was made alkaline with NaOH and extracted twice with ether. Drying (MgSO₄) and evaporation gave 2.15 g (39%) of isomeric amines 3 (purity 99% according to GLC): MS, m/z (relative intensity) 332/330 (M, 0.03/0.07), 193 (1.2), 192 (1.1), 191 (0.75), 58 (100); ¹H NMR (CDCl₃) δ 6.23 (t, minor, CH), 6.27 (t, major, CH). The configuration of the amines in the mixture was established by addition of Eu(fod)₃. The ratio of the europium-induced shifts of (minor vinyl triplet)/(major vinyl triplet) was 2.6, which leads to the conclusion that the minor triplet corresponds to the *E* isomer (cis to the pyridine coordination site, cf. ref. 17).

The isomeric amine mixture was separated by repeated preparative HPLC (SiO₂) with i-Pr₂O/MeOH/NH₃ (100:10:1) as eluent.

E Isomer. Isomeric purity was 97% after chromatography. A portion (210 mg) was precipitated as oxalate from EtOH/*i*-Pr₂O to give 190 mg of isomerically pure (>99.5%) salt, mp 190–191 °C: UV (0.1 M HCl) λ_{max} 225 nm (ϵ 20 600); ¹H NMR (CDCl₃, base) δ 6.24 (t, CH), 8.60 (narrow m, 2-pyridyl), 8.56 (dd, partly concealed, 6-pyridyl). Anal. (C₁₇H₁₉BrN₂·C₂H₂O₄) C, H, N, Br.

Z Isomer. Isomeric purity was >99% after chromatography. From 320 mg base was precipitated 330 mg of oxalate salt from aqueous EtOH/*i*-Pr₂O, mp 140–141 °C: UV (0.1 M HCl) λ_{max} 249 nm (ϵ 20 600); ¹H NMR (CDCl₃, base) δ 8.69 (dd, 6-pyridyl), 8.58 (narrow m, 2-pyridyl), 6.28 (t, CH). Anal. (C₁₇H₁₉BrN₂·C₂H₂O₄·2H₂O) C, N, Br; H: calcd, 5.51; found, 5.00.

4-(4-Bromophenyl)-N-methyl-4-(3-pyridyl)-3-buten-1-ylamine (4). To a solution of bromide 9 (5.4 g, 0.015 mol) in 70 mL of THF was added 20 mL of a solution of methylamine in THF (1:1). After being stirred overnight, the reaction mixture was subjected to the same workup procedure as above (3), which gave 1.5 g (32%) of crude amine mixture. GLC (capillary column SE 30, 230 °C) revealed three components with the following retention times: 4.99 min (19% side product 12), 5.15 min (20% 4E), and 5.36 min (42% 4Z). The ratio of 4Z and 4E is 68:32, i.e., slightly lowered from the original 74:26 in the starting bromide 9.

The amine mixture was separated by preparative HPLC (SiO₂) with i-Pr₂O/MeOH/NH₃ (100:10:1) as eluent, which gave three partially purified fractions. Each of these fractions was further

purified by preparative radial thin-layer chromatography (4-mm SiO_2 disc) with the above eluent.

E isomer: 160 mg. Isomeric purity was >95% after chromatography. From 155 mg base was prepared 100 mg of isomerically pure (>99.5%) oxalate salt by recrystallization from EtOH, mp 202–203 °C: UV (0.1 M HCl) λ_{max} 224 nm (ϵ 21 700); ¹H NMR (CDCl₃, base) δ 8.62 (narrow m, 2-pyridyl), 8.58 (dd, partly concealed, 6-pyridyl), 6.24 (t, CH); MS, m/z (relative intensity) 317/315 (M - H, 0.11/0.25), 275/273 (28/30), 274/272 (M - CH₂NHCH₃, 20/16), 193 (7.7), 192 (4.4), 191 (2.8), 44 (100); Anal. (C₁₆H₁₇BrN₂·C₂H₂O₄) C, H, N, Br.

Z isomer: 385 mg. Isomeric purity was 95% after chromatography. A portion (315 mg) was converted to 300 mg of isomerically pure (≥99.5%) oxalate salt by recrystallization from EtOH, mp 185–187 °C: UV (0.1 M HCl) λ_{max} 250 nm (ϵ 23 500); ¹H NMR (CDCl₃, base) δ 8.68 (dd, 6-pyridyl), 8.60 (narrow m, 2-pyridyl), 6.28 (t, CH); MS, same as for 4E. Anal. (C₁₆H₁₇-BrN₂·C₂H₂O₄) H, N, Br; C: calcd, 53.08, found, 53.56.

4-(4-Bromophenyl)-4-(3-pyridyl)-3-buten-1-ylamine (12): 140 mg; ¹H NMR (CDCl₃) δ 6.27 and 6.34 (overlapping t, CH), 8.6 (m, 2,6-pyridyl); MS, m/z (relative intensity) 303/301 (M – H, 0.13/0.16), 275/273 (52/57), 274/272 (45/39), 193 (25), 192 (12), 191 (8.0), 30 (100). Isopropylideneamine derivative: MS, m/z (relative intensity) 344/342 (M, 2.0/2.2), 70 (100).

Pharmacology. Accumulation of ¹⁴C-Labeled 5-HT and ³H-Labeled NE in Brain Slices.^{4c,10} Male albino mice (NMRI) weighing 18-22 g were used. The brain tissue used (40 mg) was taken from the middle part of the mouse brain and includes hypothalamus, thalamus, and midbrain. The slices (about 1-mm thick) were preincubated for 5 min at 37 °C in 2.0 mL of Krebs-Henseleit's buffer containing 1×10^{-4} M pargyline (this concentration does not inhibit the accumulation of [3H]NE or ¹⁴C]-5-HT at the experimental conditions used), 5.6 mM glucose, 1.1 mM ascorbic acid, and 1.3×10^{-4} M Na₂EDTA in an atmosphere of 6.5% CO₂ in O₂. After addition of the labeled substrates $(1 \times 10^{-7} \text{ M} [^{3}\text{H}]\text{NE} \text{ and } 1 \times 10^{-7} \text{ M} [^{14}\text{C}]\text{-5-HT})$, the incubation was continued for 5 min. The slices were rapidly removed from the incubation bottles, blotted on filter paper, and transferred to counting vials, in which they were dissolved in 1.0 mL of Soluene-350 (Packard) containing 5% distilled water. Ten milliliters of scintillation liquid (Econofluor, NEN) was added, and ³H and ¹⁴C were determined by the double-labeling technique in a Packard TriCarb scintillation spectrometer. The active accumulation of the amines was determined from the difference between those in the absence and presence of 5×10^{-4} M cocaine. The inhibition of the accumulation was calculated as a percentage of the control accumulation. Four or five concentrations of the inhibitors were determined in quadruplicate. The standard error of the mean at each concentration was less than 10%. The IC_{50} values were determined from semilogarithmic plots.

The in vivo inhibition of the amine accumulation was determined by the same technique as described above. The compounds were injected intraperitoneally, and the animals were sacrificed 60 min later. Brain slices were prepared and incubated with the labeled amines. Three or four different doses were examined with four mice in each dose. The standard error of the mean at each concentration was less than 10%. ED_{50} values were estimated from semilogarithmic plots.

Accumulation of ¹⁴C-Labeled 5-HT and ³H-Labeled NE in Synaptosomes.¹⁹ Sprague–Dawley rats weighing 160–200 g were used. Crude synaptosome preparations from rat cerebral cortex were made by homogenizing the tissues in 10 volumes of ice-cold 0.32 M sucrose with all-glass Potter-Elvehjem's homogenizers. The homogenates were centrifuged at 800g at 2 °C for 10 min. The supernatants were centrifuged at 12000g at 2 °C for 10 min, and the pellets were rehomogenized in 0.32 M sucrose to the original volume. The incubation of the preparations with [14C]-5-HT + [³H]NE with final concentrations of 50 nM of each amine was performed in a Micronic PPN Storage-Block-96 (Flow Laboratories) with 8×12 wells by using two rows of each incubation. Nine different concentrations of the test compounds in duplicates were examined at each incubation; 50 μ L of the synaptosomal preparation, 400 µL of the Krebs-Henseleit's buffer, pH 7.4, containing 5.6 mM glucose, 1.1 mM ascorbic acid, 0.13 mM Na_2EDTA , and 50 μM pargyline and 25 μL of the inhibitor or distilled water were added to the wells. The solutions were mixed

by vortexing the block for 10 s. After a 10-min preincubation at 37 °C in a water bath, 25 μ L of the solutions of the radioactively labeled amines was added to the two rows with a Titrertec Multichannel pipette, type 12-channel (Flow Laboratories). The reaction was immediately started by vortexing the block for 10 s on a Super-Mixer, and the incubation was continued for 2 min at 37 °C. The uptake reaction was stopped by filtration and washing for 15 s with ice-cold 0.15 M NaCl through a Whatman GF/B glass filter paper in a 24-channel cell harvester (Brandel) with use of the standard harvesting probe. The filters were left to dry at room temperature for about 1 h. The punched filters were transformed to counting vials, 10 mL of the scintillation liquid (Aquasol, NEN) was added, and vials were shaken and allowed to stand for 1 h before counting. The radioactivity was measured in a Packard TriCarb liquid scintillation photometer. The active uptake of the amines was defined as the difference between the accumulation of the radioactivity in the absence (triplicates) and the presence (triplicates) of selective uptake inhibitors, determined at each incubation. These inhibitors were citalopram (0.3 μ M) for the serotonin uptake and maprotiline (1 μ M) for the norepinephrine uptake. The inhibition was calculated in percent of the active uptake. The IC_{50} values were obtained from log concentration-response curves. The SEM of the control values (n = 24) was for the NE uptake $\pm 0.9\%$ of the mean and for the 5-HT uptake $\pm 3\%$. The difference between the duplicates expressed in percent of the mean was determined for the nine concentrations in each experiment. The mean (\pm SEM) of this difference was for the NE uptake 6.4 \pm 1.6% or less and for the 5-HT uptake 7.2 \pm 2.0% or less.

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Registry No. (Z)-1, 56775-88-3; (E)-1, 56775-89-4; (Z)-3, 112969-63-8; (Z)-3.oxalate, 112969-66-1; (E)-3, 112969-64-9; (E)-3.oxalate, 112969-65-0; (Z)-4, 112969-67-2; (Z)-4.oxalate, 112969-68-3; (E)-4, 112969-69-4; (E)-4.oxalate, 112969-70-7; 7, 14548-45-9; 8, 112969-71-8; (Z)-9, 112969-72-9; (E)-9, 112969-73-0; 10, 112969-74-1; (E)-11, 112969-75-2; (Z)-11, 112969-76-3; 12, 112969-77-4; NE, 51-41-2; 5-HT, 50-67-9; PCl₅, 10026-13-8; PCl₃, 7719-12-2; SOCl₂, 7719-09-7; HCl, 7647-01-0; ZnCl₂, 7646-85-7; PBr₅, 7789-60-8; HBr, 10035-10-6; HOAc, 64-19-7; cyclopropyl bromide, 4333-56-6.

Novel Calcium Antagonists. Synthesis and Structure–Activity Relationship Studies of Benzothiazoline Derivatives

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A series of novel compounds having a benzothiazoline skeleton was studied for their structure-activity relationship (SAR) with respect to Ca^{2+} antagonistic activity. As test compounds, analogues of 3-acyl-2-arylbenzothiazolines (3) were synthesized. Benzothiazoline derivatives (3) exerted higher Ca^{2+} antagonistic activity than the corresponding thiazolidine derivatives (2). Effects of substituents R_1-R_4 , the substitution position of the aminoalkoxy group and R_2 , and the length of the methylene chain on biological activities were examined. Compound 4 [3-acetyl-2-[5-methoxy-2-[4-[N-methyl-N-(3,4,5-trimethoxyphenethyl)amino]butoxy]phenyl]benzothiazoline hydrochloride] showed a potent Ca^{2+} antagonistic activity in vitro and dual inhibition on the fast Na⁺ inward channel and the slow Ca^{2+} inward channel in Langendorff perfused rabbit hearts. Compound 4 also showed a long-acting hypotensive effect in spontaneously hypertensive rats and prevented acute pulmonary thrombotic death in mice.

 Ca^{2+} antagonists are highly valued as therapeutic agents for essential hypertension and angina pectoris because of their excellent profiles.¹⁻¹⁰ There are only a few Ca²⁺

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