3324-71-8; MeOCONCS, 35266-49-0; $PrNH_2$, 107-10-8; *i*-$PrNH_2$, 75-31-0; $BuNH_2$, 109-73-9; *t*-$BuNH_2$, 75-64-9; $H_3C(CH_2)_4NH_2$, 110-58-7; $H_2C{=}CHCH_2NH_2$, 107-11-9; $PhCH_2NH_2$, 100-46-9; c-$C_5H_9NH_2$, 1003-03-8; $HOCH_2CH_2NH_2$, 141-43-5; $HO(CH_2)_3NH_2$, 156-87-6; $Me_2N(CH_2)_3NH_2$, 109-55-7; H_2NCN, 420-04-2; $PhNH_2$, 62-53-3; c-$C_4H_7NH_2$, 2516-34-9; $MeO(CH_2)_2NH_2$, 109-85-3; $MeO(CH_2)_3NH_2$, 5332-73-0; $EtO(CH_2)_2NH_2$, 110-76-9; $Ph(CH_2)_2NH_2$, 64-04-0; $H_3CCH(OH)CH_2NHMe$, 16667-45-1; $MeS(CH_2)_2NH_2$, 18542-42-2; $AcNH(CH_2)_2NH_2$, 1001-53-2; $MeONH_2$, 67-62-9; $MeNH_2$, 74-89-5; $H_2N(CH_2)_2NH_2$, 107-15-3; $MeNH(CH_2)_2NH_2$, 109-81-9; $H_2NC(CH_3)_2CH_2NH_2$, 811-93-8; $MeNH(CH_2)_2NHMe$, 110-70-3; $H_2N(CH_2)_3NH_2$, 109-76-2; $H_2NCH_2C(OMe)_2$, 22483-09-6; guanidine carbonate, 100224-74-6; [5-(2-iodophenyl)-1,3,4-thiadiazol-2-yl]cyanamide, 113113-50-1; [5-(2,4-dimethylphenyl)-1,3,4-thiadiazol-2-yl]cyanamide, 113113-51-2; [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; *S*-methyl[5-(2,4-dimethylphenyl)-1,3,4-thiadiazol-2-yl]dithiocarbamate, 113113-45-4; [5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]formamide, 113113-46-5; 2-(methylamino)-5-(2-methylphenyl)-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

Thomas Högberg,*† Svante B. Ross,† Peter Ström,† Gary L. Grunewald,*‡ Mary W. Creese,‡ and Jeffrey D. Bunce‡

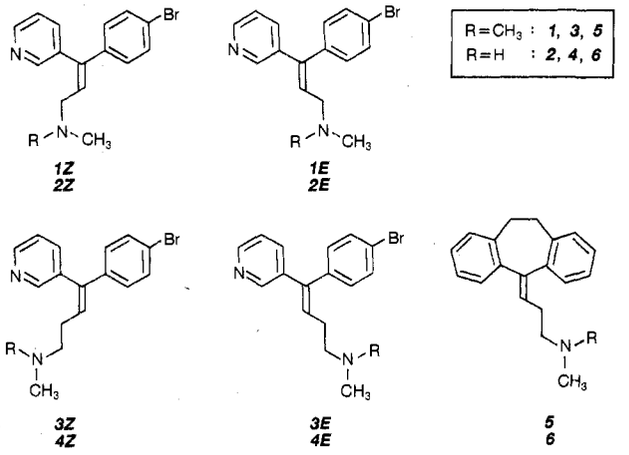
Research and Development Laboratories, Astra Alab AB, S-151 85 Södertälje, Sweden, and Department of Medicinal Chemistry, University of Kansas, Lawrence, Kansas 66045. *Received June 29, 1987*

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 (**3*Z***, **4*Z***) were specific 5-HT uptake inhibitors in analogy with the corresponding allylic derivatives zimeldine (**1*Z***) and norzimeldine (**2*Z***). Likewise, the selectivity profile of the homoallylic (**3*E***, **4*E***) and the allylic (**1*E***, **2*E***) 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 (**4*Z***) 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 **4*Z*** compared to **2*Z***.

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 (**1*Z***, 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–Barrē 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 **1*Z*** and **2*Z*** are selective neuronal 5-HT uptake inhibitors, whereas in the *E* series, especially the secondary amine **2*E*** is more active as a norepinephrine (NE) uptake inhibitor (Chart I). It is

Chart I. Structures of Allylic and Homoallylic Amines Investigated (**1*Z***, zimeldine; **2*Z***, norzimeldine; **5**, amitriptyline; and **6**, nortriptyline)

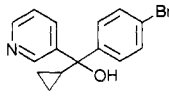


(1) (a) Kuhn, R. *Am. J. Psychiatry* **1958**, *115*, 459–464. (b) Hollister, L. E. *Annu. Rev. Pharmacol. Toxicol.* **1986**, *26*, 23–37.
(2) (a) Sugrue, M. F. *Pharmacol. Ther.* **1983**, *21*, 1–33. (b) Ögren, S.-O.; Fuxe, K.; Agnati, L. *Pharmacopsychiatry* **1985**, *18*, 209–213. (c) Stahl, S. M.; Palazidou, L. *Trends Pharmacol. Sci.* **1986**, *7*, 349–354.

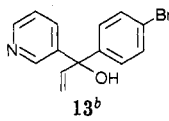
† Astra Alab AB.
‡ University of Kansas.

0022-2623/88/1831-0913$01.50/0

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



8



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		

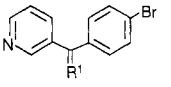
[a] The alcohol 8 or 13 (0.2 mmol) was treated with excess halide in 5 mL of CH_2Cl_2 during 3 h at room temperature. In the case of 13, the allylic chloride formed was reacted with excess $HNMe_2$ and analyzed as amine 1. In the case of 8, the solution of halide 9 or 10 was washed with 1 M Na_2CO_3 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. [c] Three equivalents of halide was used with 8 and 1.5–2 equiv of halide with 13. [d] No conversion with anhydrous HCl. [e] Ten-hour 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 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**, and **4Z**), all being fairly specific neuronal uptake inhibitors, was made in order to see if pharmacological activity and selectivity correlate with conformational preference.

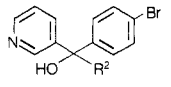
Chemistry

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



	R^1
7	=O
9	=CH–CH_2CH_2Br
10	=CH–CH_2CH_2Cl
11	=CH–CH=CH_2
12	=CH–$CH_2CH_2NH_2$



	R^2
8	c-C_3H_5
13	CH=CH_2

contrast to the allylic rearrangement of **13**, no marked

(3) Baldessarini, R. J. *The Pharmacological Basis of Therapeutics*, 7th ed.; Gilman, A. G., Goodman, L. S., Rall, T. W., Murad, F., Eds.; MacMillan: New York, 1985; pp 413–423.

(4) (a) Wong, D. T.; Horng, J. S.; Bymaster, F. P.; Hauser, K. L.; Molloy, B. B. *Life Sci.* **1974**, *15*, 471–479. (b) Buus Lassen, J.; Squires, R. F.; Christensen, J. A.; Molander, L. *Psychopharmacology* **1975**, *42*, 21–26. (c) Ross, S. B.; Ögren, S.-O.; Renyi, A. L. *Acta Pharmacol. Toxicol.* **1976**, *39*, 152–166. (d) Sugrue, M. F.; Goodlet, I.; Mireylees, S. E. *Eur. J. Pharmacol.* **1976**, *40*, 121–130. (e) Le Fur, G.; Uzan, A. *Biochem. Pharmacol.* **1977**, *26*, 497–503. (f) Hyttel, J. *Psychopharmacology* **1977**, *51*, 225–233. (g) Ross, S. B.; Renyi, A. L. *Neuropharmacology* **1977**, *16*, 57–63. (h) Lindberg, U. H.; Thorberg, S.-O.; Bengtsson, S.; Renyi, A. L.; Ross, S. B.; Ögren, S.-O. *J. Med. Chem.* **1978**, *21*, 448–456. (i) Waldmeier, P. C.; Baumann, P. A.; Maitre, L. *J. Pharmacol. Exp. Ther.* **1979**, *211*, 42–49.

(5) Lemberger, L.; Fuller, R. W.; Zerbe, R. L. *Clin. Pharmacol.* **1985**, *8*, 299–317.

(6) (a) Coopen, A. *Br. J. Psychiatry* **1967**, *113*, 1237–1264. (b) Carlsson, A.; Corrodi, H.; Fuxe, K.; Hökfelt, T. *Eur. J. Pharmacol.* **1969**, *5*, 357–366. (c) Lapin, I. P.; Oxenkrug, G. F. *Lancet* **1969**, *1*, 132–136. (d) Van Praag, H. M.; Korf, J. *Psychopharmacology* **1971**, *19*, 148–152. (e) Van Praag, H. M. *Pharmacopsychiatry* **1974**, *7*, 281–292. (f) Carlsson, A. *Br. J. Clin. Pract.* (Symposium Suppl. 19) **1982**, 19–21.

(7) (a) Heel, R. C.; Morley, P. A.; Brogden, R. N.; Carmine, A. A.; Speight, T. M.; Avery, G. S. *Drugs* **1982**, *24*, 169–206; *Curr. Ther.* **1983**, *24*, 11. (b) Gottfries, C.-G., Ed. *Acta Psychiatr. Scand., Suppl.* **1983**, *68* No. 308. (c) *Symposium: Depression and Antidepressants–Recent Events*; Dresse, A.; Deberdt, R.; Mendlewicz, J.; Schutyser, P., Eds.; Excerpta Medica: Amsterdam, 1983. (d) Ochsenfahrt, H. *Int. Med.* (Suppl. No. 10) **1984**, 2–7.

(8) (a) Fagius, J.; Osterman, P. O.; Sidēn, Å.; Wiholm, B.-E. *J. Neurol., Neurosurg. Psychiatry* **1985**, *48*, 65–69. (b) Dexter, S. L. *Hum. Toxicol.* **1984**, *3*, 141–143.

(9) Ögren, S.-O.; Ross, S. B.; Hall, H.; Holm, A. C.; Renyi, A. L. *Acta Psychiatr. Scand., Suppl. 290*, **1981**, *63*, 127–151.

(10) Högberg, T.; Ulff, B.; Renyi, A. L.; Ross, S. B. *J. Med. Chem.* **1981**, *24*, 1499–1507.

(11) Lundström, J.; Högberg, T.; Gosztonyi, T.; de Paulis, T. *Arzneim.-Forsch.* **1981**, *31*, 486–494.

(12) Ross, S. B. *Pharmacology* **1980**, *21*, 123–131.

(13) Kaiser, C.; Setler, P. E. *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; Wiley: New York, 1981; Part III, pp 997–1067.

(14) Jones, G.; Maisey, R. F.; Somerville, A. R.; Whittle, B. A. *J. Med. Chem.* **1971**, *14*, 161–164.

(15) (a) Carnmalm, B.; de Paulis, T.; Högberg, T.; Johansson, L.; Persson, M.-L.; Thorberg, S.-O.; Ulff, B. *Acta Chem. Scand., Ser. B.* **1982**, *B36*, 91–99. (b) Högberg, T.; Ulff, B. *J. Org. Chem.* **1984**, *49*, 4209–4214. (c) Bäckvall, J.-E.; Nordberg, R. E.; Nyström, J.-E.; Högberg, T.; Ulff, B. *J. Org. Chem.* **1981**, *46*, 3479–3483. (d) Högberg, K.; Lindgren, J.-E.; Högberg, T.; Ulff, B. *Acta Pharm. Suec.* **1979**, *16*, 299–308.

(16) Hoffsommer, R. D.; Taub, D.; Wendler, N. L. *J. Org. Chem.* **1962**, *27*, 4134–4137.

Table II. Configurational Assignments of Homoallylic Amines 3 and 4 by Means of UV (0.1 M HCl) and ^{1}H NMR ($CDCl_3$) Spectroscopy

	UV		^{1}H NMR, ppm		
no.	λ_{max}, nm	ϵ_{max}	2-py	6-py	vinyl
1*Z*[a]	250	19700	8.46	8.60	6.30
1*E*[a]	219	21900	8.53	8.50	6.27
3*Z*	249	20600	8.58	8.69	6.28
3*E*	225	20600	8.60	8.56	6.24
4*Z*	250	23500	8.60	8.68	6.28
4*E*	224	21700	8.62	8.58	6.24

[a] Stereochemistry unambiguously determined by means of X-ray single-crystal analysis (1*Z*)[18] and lanthanide-induced shifts in ^{1}H NMR (1*Z*,1*E*)[17] analysis.

Table III. Inhibition of the Accumulation of (−)-[^{3}H]Norepinephrine (NE) and [^{14}C]-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}, μM			slices, mouse: ex vivo ED_{50}, μmol/kg, ip	
compound	amine	side chain	NE	5-HT	ratio[b]	NE	5-HT	ratio[b]	NE	5-HT
zimeldine (1*Z*)	tert	allyl	3.2	0.10	32	24[d]	1.7[d]	14	>98 (26%)[c,d]	49[d]
norzimeldine (2*Z*)	sec	allyl	0.24	0.038	6.3	1.5[d]	0.10[d]	15	>102 (38%)[d]	19[d]
3*Z*	tert	homoallyl	22.5	0.50	45	>24 (20%)	0.90	>27	>95 (15%)	95 (57%)
4*Z*	sec	homoallyl	6.6	0.24	28	>25 (20%)	0.50	>50	>98 (1%)	>98 (35%)
1*E*	tert	allyl	0.15	0.22	0.68	6.1[d]	6.1[d]	1.0	25[d]	>98 (36%)[d]
2*E*	sec	allyl	0.0046	0.080	0.058	0.8[d]	2.5[d]	0.32	25[d]	102[d]
3*E*	tert	homoallyl	1.4	2.6	0.54	7.8	7.1	1.1	95 (18%)	>95 (11%)
4*E*	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%)

[a] See the Experimental Section for details. [b] Selectivity expressed as ratio between NE and 5-HT uptake inhibition. [c] The values in parentheses indicate the inhibition at the highest dose level in percent. [d] Data taken from ref 10.

difference in the stereochemical outcome in the formation of **10** was observed for the different chlorination reagents (PCl_5, PCl_3, $SOCl_2$, $HCl/ZnCl_2$), i.e., about 67% of the *Z* isomer **10** was produced. As can be seen, the bromination reagents (PBr_5, PBr_3, 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 **3***Z* and **3***E* 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 separations 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 **4***Z* (42%), **4***E* (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 **4***Z* and **4***E* 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 **3***E* and **3***Z* were established by analysis of the europium-induced shifts in ^{1}H 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 ^{1}H NMR spectroscopy as shown in Table II.

Inhibition of NE and 5-HT Accumulation

Methods. The accumulation of ^{3}H-labeled norepinephrine (NE) and ^{14}C-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 IC_{50} and ED_{50} 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 (1*Z*) and the secondary amine **2***Z*, both exhibit large NE/5-HT ratios, although **2***Z* is considerably more potent than 1*Z*.[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-

(17) Högberg, T. *Acta Chem. Scand., Ser. B* **1980**, *B34*, 629–632.
(18) Abrahamsson, S.; Carlsson, A.; Carnmalm, B.; Dahlén, B. *Acta Chem. Scand., Ser. A* **1976**, *A30*, 609–613.
(19) Florvall, L.; Kumar, Y.; Ask, A.-L.; Fagervall, I.; Renyi, L.; Ross, S. B. *J. Med. Chem.* **1986**, *29*, 1406–1412.

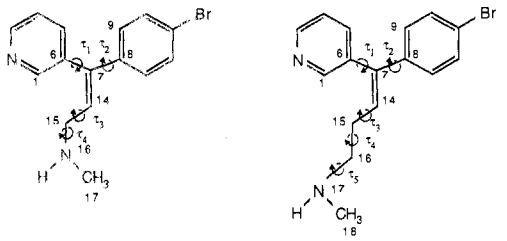


Figure 1. Torsion angles for the allylic and homoallylic amines subjected to molecular mechanics calculations: $\tau_1 = C_1$–C_6–C_7–C_{14}, $\tau_2 = C_9$–C_8–C_7–C_{14}, $\tau_3 = C_7$–C_{14}–C_{15}–$C_{16}(N_{16})$, $\tau_4 = C_{14}$–C_{15}–$C_{16}(N_{16})$–$N_{17}(C_{17})$, $\tau_5 = C_{15}$–C_{16}–N_{17}–C_{18} (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 CAMSEQ[20] 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 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.

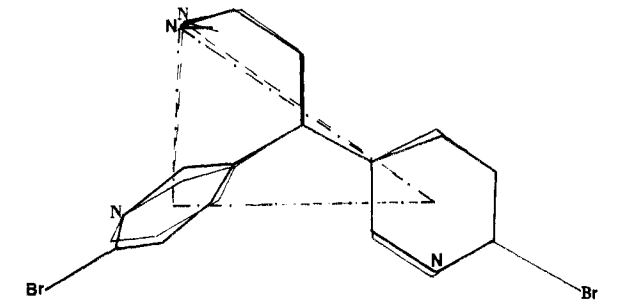


Figure 2. Molecular graphics (SYBYL)[24] overlay drawing of norzimeldine (**2Z**), light lines) in conformation 3 and (*E*)-norzimeldine (**2E**, heavy lines) in conformation 4. The aryl ring centers and aliphatic nitrogens were subjected to a least-squares fit (dashed lines).

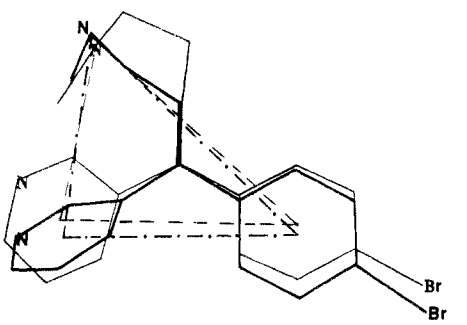


Figure 3. Molecular graphics (SYBYL)[24] overlay drawing of norzimeldine (**2Z**, heavy lines) in conformation 1 and homonorzimeldine (**4Z**, light lines) in conformation 3. The aryl ring centers and aliphatic nitrogens were subjected to a least-squares fit (dashed lines).

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 SYBYL[24] 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) $\approx$

(20) (a) Weintraub, H. J. R.; Hopfinger, A. J. *Int. J. Quantum Chem., Quantum Biol. Symp.* **1975**, *2*, 203–208. (b) Weintraub, H. J. R. Ph.D. Dissertation, Case Western Reserve University, Cleveland, OH, 1975. (c) Potenzone, R.; Cavicci, E.; Weintraub, H. J. R.; Hopfinger, A. J. *Comput. Chem.* **1977**, *1*, 187–194.

(21) Creese, M. W.; Grunewald, G. L. *J. Am. Chem. Soc.* **1983**, *105*, 2463–2469.

(22) Grunewald, G. L., Creese, M. W. *Drug Design Delivery* **1986**, *1*, 23–37.

(23) Poland, D.; Scheraga, H. A. *Biochemistry* **1967**, *6*, 3791–3795.

(24) Available from Tripos Associates, St. Louis, MO. See, for example: Marshall, G. R.; Van Opdenbosch, N.; Font, J. "Systematic search of conformational space: use and visualization"; *Second SCI-RSC Medicinal Chemistry Symposium*. Special Publication No. 50, Emmett, J. C., Ed.; The Royal Society of Chemistry: London, 1983; pp 99–108.

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

compound		torsion angles,[a] deg τ_1	τ_2	τ_3	τ_4	τ_5	energy above global min, kcal mol^{-1}	distances, Å: phenyl to pyridyl centers	phenyl center to amine	pyridyl center to 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
							maximum deviation 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
							maximum deviation 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
							maximum deviation 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 τ_2/τ_1) ≈ 120° - 140°/170° - 180°. 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 SYBYL[24] 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. ^{1}H NMR spectra were recorded on a Varian EM 360 A with Me_4Si 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 ±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 (4-bromobenzoyl)-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 NH_4Cl (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 ($MgSO_4$) 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*-Pr_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: ^{1}H NMR

($CDCl_3$) δ 0.55 (m, 4, CH_2CH_2), 1.49 (m, 1, CH), 4.35 (s, 1, OH), 7.1–7.7 (m + AA'BB', 5, aromatic), 7.82 (dt, 1, 4-pyridyl), 8.34 (dd, 1, 6-pyridyl), 8.53 (d, 1, 2-pyridyl); MS, *m/z* (relative intensity) 305/303 (M, 1.6/1.6), 277/275 (M – C_2H_4, 94/100), 264/262 (M – C_3H_5, 25/25), 196 (9), 185/183 (23/23), 157/155 (12/13), 106 (91). Anal. ($C_{15}H_{14}BrNO$) C, H, N, Br, O.

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 CH_2Cl_2 was cooled in an ice bath, and PBr_3 (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 Na_2CO_3. After dilution with water, the mixture was extracted with CH_2Cl_2 twice. The organic layer was washed with water and brine, dried ($MgSO_4$), and evaporated to give 6.20 g (99%) of an oil. GLC showed the *Z*/*E* isomeric ratio of 74:26: ^1H NMR ($CDCl_3$) δ 2.72 (app q, 2, CH_2), 3.50 (t, 2, CH_2Br), 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 $NaHCO_3$. 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% **3*E***) and 4.10 min (39% **3*Z***), 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 CH_2Cl_2 and washed twice with 2 M NaOH to remove acetic acid. Drying ($MgSO_4$) 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 ($MgSO_4$) 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 ($CDCl_3$) 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 (SiO_2) with *i*-Pr_2O/MeOH/NH_3 (100:10:1) as eluent.

***E* Isomer.** Isomeric purity was 97% after chromatography. A portion (210 mg) was precipitated as oxalate from EtOH/*i*-Pr_2O 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 ($CDCl_3$, base) δ 6.24 (t, CH), 8.60 (narrow m, 2-pyridyl), 8.56 (dd, partly concealed, 6-pyridyl). Anal. ($C_{17}H_{19}BrN_2 \cdot C_2H_2O_4$) 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*-Pr_2O, mp 140–141 °C: UV (0.1 M HCl) λ_{max} 249 nm (ε 20 600); ^1H NMR ($CDCl_3$, base) δ 8.69 (dd, 6-pyridyl), 8.58 (narrow m, 2-pyridyl), 6.28 (t, CH). Anal. ($C_{17}H_{19}BrN_2 \cdot C_2H_2O_4 \cdot 2H_2O$) 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% **4*E***), and 5.36 min (42% **4*Z***). The ratio of **4*Z*** and **4*E*** 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 (SiO_2) with *i*-Pr_2O/MeOH/NH_3 (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 ($CDCl_3$, 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 – CH_2NHCH_3, 20/16), 193 (7.7), 192 (4.4), 191 (2.8), 44 (100); Anal. ($C_{16}H_{17}BrN_2 \cdot C_2H_2O_4$) 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 ($CDCl_3$, base) δ 8.68 (dd, 6-pyridyl), 8.60 (narrow m, 2-pyridyl), 6.28 (t, CH); MS, same as for **4*E. Anal. ($C_{16}H_{17}BrN_2 \cdot C_2H_2O_4$) 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 ($CDCl_3$) 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 ^{14}C-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 [^{14}C]-5-HT at the experimental conditions used), 5.6 mM glucose, 1.1 mM ascorbic acid, and 1.3×10^{-4} M Na_2EDTA in an atmosphere of 6.5% CO_2 in O_2. After addition of the labeled substrates (1×10^{-7} M [^3H]NE and 1×10^{-7} M [^{14}C]-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 ^{14}C 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 ^{14}C-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 800*g* at 2 °C for 10 min. The supernatants were centrifuged at 12000*g* 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 [^{14}C]-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 μL 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 μL 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 μM) for the serotonin uptake and maprotiline (1 μM) 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 ±0.9% of the mean and for the 5-HT uptake ±3%. The difference between the duplicates expressed in percent of the mean was determined for the nine concentrations in each experiment. The mean (±SEM) of this difference was for the NE uptake 6.4 ± 1.6% or less and for the 5-HT uptake 7.2 ± 2.0% or less.

Acknowledgment. We thank Dr. Lucy Rényi and Ingrid Fagervall for performing uptake experiments. Research support was provided by the National Institutes of Health (Grant GM22988), the University of Kansas General Research Fund, and by a grant from the State of Kansas Advanced Technology Commission (with matching funds provided by Astra Alab). J.D.B. was the recipient of a predoctoral traineeship (NIH Grant GM 07775). A gift of the SYBYL software to the University of Kansas from Tripos Associates, St. Louis, MO, is gratefully acknowledged.

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; PCl_5, 10026-13-8; PCl_3, 7719-12-2; $SOCl_2$, 7719-09-7; HCl, 7647-01-0; $ZnCl_2$, 7646-85-7; PBr_5, 7789-69-7; PBr_3, 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

Koji Yamamoto,* Masanobu Fujita, Keizo Tabashi, Yoichi Kawashima, Eishin Kato, Masayuki Oya, Tadashi Iso, and Jun-ichi Iwao

Research Laboratory, Santen Pharmaceutical Co., Ltd., 3-9-19, Shimoshinjo-cho, Higashiyodogawa-ku, Osaka, Japan.
Received January 28, 1987

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 Ca^{2+} antagonists on the market (**5**–**8**), but their structures are fundamentally different from each other.[11] The structure–activity relationships (SAR) of 1,4-dihydropyridine derivatives[2,12-14] and verapamil derivatives[15-17] have been

(1) Fleckenstein, A. *Annu. Rev. Pharmacol. Toxicol.* **1977**, *17*, 149.
(2) Triggle, D. J.; Swamy, V. C. *Chest* (Suppl.) **1980**, *78*, 174.
(3) (a) Antman, E. M.; Stone, P. H.; Muller, J. E.; Braunwald, E. *Ann. Intern. Med.* **1980**, *93*, 875. (b) Stone, P. H.; Antman, E. M.; Muller, J. E.; Braunwald, E. *Ibid.* **1980**, *93*, 886.
(4) (a) McAllister, R. G., Jr. *Prog. Cardiovasc. Dis.* **1982**, *25*, 83. (b) Singh, B. N.; Hecht, H. S.; Nademanee, K.; Chew, C. Y. C. *Ibid.* **1982**, *25*, 103. (c) Talano, J. V.; Tommaso, C. *Ibid.* **1982**, *25*, 141. (d) Thêroux, P.; Waters, D. D.; Latour, J.-G. *Ibid.* **1982**, *25*, 157.
(5) (a) Aoki, K.; Kawaguchi, Y.; Sato, K.; Kondo, S.; Yamamoto, M. *J. Cardiovasc. Pharmacol.* **1982**, *4*, S298. (b) Muiesan, G.; Agabiti-Rosei, E.; Castellano, M.; Alicandri, C. L.; Corea, L.; Fariello, R.; Beschi, M.; Romanelli, G. *Ibid.* **1982**, *4*, S325. (c) Thibonnier, M.; Corvol, P.; Banzet, O.; Menard, J. *Ibid.* **1982**, *4*, S335. (d) McAllister, R. G., Jr. *Ibid.* **1982**, *4*, S340. (e) Bühler, F. R.; Hulthén, U. L.; Kiowski, W.; Müller, F. B.; Bolli, P. *Ibid.* **1982**, *4*, S350. (f) MacGregor, G. A.; Rotellar, C.; Markandu, N. D.; Smith, S. J.; Segnella, G. A. *Ibid.* **1982**, *4*, S358.
(6) Fleckenstein, A. *Circ. Res. Suppl.* **1983**, *52*, I-3.
(7) Janis, R. A.; Triggle, D. J. *J. Med. Chem.* **1983**, *26*, 775.
(8) Cauvin, C.; Loutzenhiser, R.; Breeman, C. *Annu. Rev. Pharmacol. Toxicol.* **1983**, *23*, 373.
(9) (a) Singh, B. N.; Nademanee, K.; Baky, S. H. *Drugs* **1983**, *25*, 125. (b) Spivack, C.; Ocken, S.; Frishman, W. H. *Ibid.* **1983**, *25*, 154. (c) Thêroux, P.; Taeymans, Y.; Waters, D. D. *Ibid.* **1983**, *25*, 178.
(10) Schwartz, A.; Triggle, D. J. *Annu. Rev. Med.* **1984**, *35*, 325.
(11) Nayler, W. G. *Int. J. Cardiol.* **1983**, *3*, 391.
(12) Rodenkirchen, R.; Bayer, R.; Steiner, R.; Bossert, F.; Meyer, H.; Möller, E. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1979**, *310*, 69.
(13) Mannhold, R.; Rodenkirchen, R.; Bayer, R. *Prog. Pharmacol.* **1982**, *5*, 9.
(14) Fossheim, R.; Svarteng, K.; Mostad, A.; Romming, C.; Shefter, E.; Triggle, D. J. *J. Med. Chem.* **1982**, *25*, 126.
(15) Mannhold, R.; Steiner, R.; Haas, W.; Kaufmann, R. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **1978**, *302*, 217.
(16) Höltie, H.-D. *Arch. Pharm. (Weinheim, Ger.)* **1982**, *315*, 317.

0022-2623/88/1831-0919$01.50/0