An inoculum of *C. albicans* was prepared by suspending the yeast cells grown for 48 h in Sabouraud's dextrose broth. Inocula of *A. fumigatus* and *T. asteroides* were prepared by suspending the conidia grown for 14 days in the same broth containing Tween 80 at 0.1%.

Bacterial Strains. *Staphylococcus aureus, Streptococcus pyogenes, Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* were tested. These strains, except *S. pyogenes,* were grown overnight at 37 °C on Heart Infusion agar slants. *S. pyogenes* was grown on a Brain–Heart Infusion agar slant. Inocula were prepared by suspending the growth in Mueller–Hinton broth.

Preparation of Drugs. Stock solutions of *o*-carborane derivatives were prepared at a concentration of 1 mg/mL. Methyl alcohol was used to solubilized the compound, which were insoluble in water.

Determination of MIC. Minimum inhibitory concentrations (MICs) were determined with the microtiter system. Inocula of fungal and bacterial strains were equally adjusted to 1×10^5 colony forming units per milliliter. Sabouraud's dextrose broth was used as the testing medium for fungi, and Mueller–Hinton broth was used for bacteria. The drug concentrations ranged from 100 to 0.01 μg/mL using the automatic twofold serial dilution technique. The final volume in the microtiter well was 0.05 mL. The concentration of methyl alcohol never exceeded 2%, which showed no inhibitory effect on any of the test organisms. After dilution, the microtiter plates were sealed with a cellophane membrane and incubated at 37 °C for 48 h. The MIC was defined as the lowest concentration of drug at which no visible fungal or bacterial growth was observed.

Synthesis of Pyridylallylamines Related to Zimelidine and Their Inhibition of Neuronal Monoamine Uptake

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Analogues of the antidepressant agent zimelidine [**6**, (*Z*)-3-(4-bromophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine], a selective inhibitor of neuronal 5-hydroxytryptamine reuptake, were synthesized by several routes with the aim of obtaining compounds having a cis configuration (with respect to pyridyl and allylamine). Two methods utilized suitably substituted benzoylpyridines as starting materials. In two other routes, the bromine in **6** was either directly displaced (CN) or converted via the corresponding lithio derivative to H, Cl, I, Me, $SiMe_3$, and SMe. The configurations were determined by UV, ^1H NMR, and lanthanide-induced shifts in ^1H NMR. The compounds were evaluated as uptake inhibitors by measuring the accumulation of [^3H]noradrenaline and 5-hydroxy[^{14}C]tryptamine in mouse brain slices (in vitro and in vivo). Para substitution favored 5-hydroxytryptamine activity and ortho substitution favored NA activity in the cis series. The in vitro effect on 5-hydroxytryptamine was rather insensitive to variations in the para substituent, whereas pronounced effects in vivo were observed only with Cl, Br (**6**), and I.

The possible involvement of 5-hydroxytryptamine (5-HT) in the etiology of endogenous depression[1-4] has aroused interest in the development of selective inhibitors of neuronal 5-HT reuptake.[5-12] One such compound, zimelidine [**6**, (*Z*)-3-(4-bromophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine], has been shown in double blind clinical studies to possess antidepressive action similar to that of tricyclic antidepressant drugs.[13-16] Furthermore, there are indications of a low incidence of adverse effects of zimelidine.[13,14] This might be explained by the negligible action of **6** on most neurotransmitter receptors in the brain and the periphery (α_1-, α_2-, and β-adrenergic; 5-HT; histamine H_1 and H_2; muscarinic).[17,18] The lack of significant interaction with ethanol, barbiturates, and benzodiazepines

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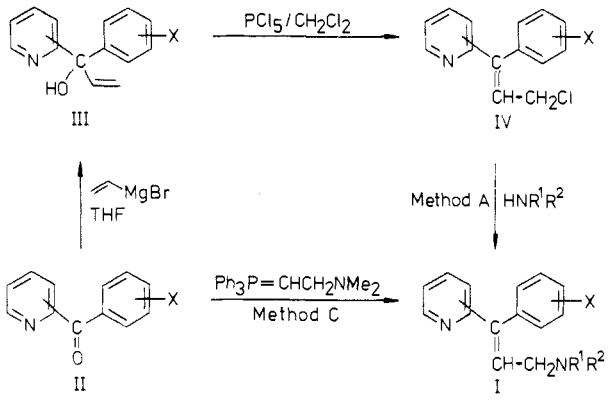
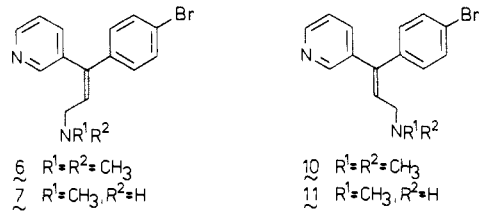
Scheme I



and the minor cardiovascular effects of **6** are also noteworthy.[17,18]

Zimelidine (**6**) and particularly its primary metabolite,



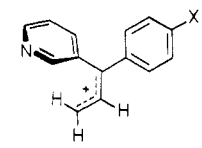
6 $R^1=R^2=CH_3$
7 $R^1=CH_3, R^2=H$
10 $R^1=R^2=CH_3$
11 $R^1=CH_3, R^2=H$

the secondary amine norzimelidine (**7**),[18-20] are potent and selective inhibitors of the neuronal uptake of 5-HT in the rat brain.[17,21] These compounds (**6** and **7**) have the pyridyl and the allylamine moieties oriented in a cis relation (*Z* configuration).[20,22-24] The trans isomer of zimelidine (**10**) is a nonselective inhibitor of 5-HT and noradrenaline (NA) uptake in rat hypothalamic synaptosomes, whereas the corresponding secondary amine **11** is a potent and selective NA uptake inhibitor.[21] (See also Table V.)

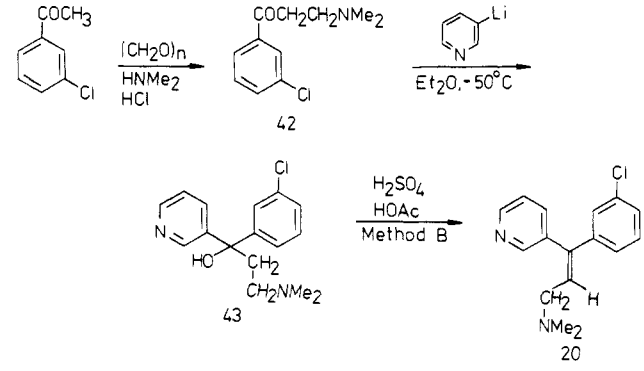
The pharmacological effects of zimelidine prompted further examination of this type of compound. We have synthesized 3-phenyl-3-pyridylallylamines having various substituents in the phenyl ring and determined their inhibition of the neuronal uptake of 5-HT and NA in mouse brain slices. Since the cis pair **6** and **7** exert almost opposite inhibitory effects to the trans pair **10** and **11**, care has been taken to separate the cis–trans isomers and determine the configuration of the new compounds. This paper is mainly concerned with the substituent effects in compounds having the pyridyl and allylamine functions in the cis orientation, i.e., the same as in zimelidine.

Chemistry. The syntheses of **6**, **7**, **10**, and **11** have recently been described.[25] One efficient route to the cis isomers **6**, **7**, **8**, and **9** (Table I) using an allylic rearrangement of **33** (Table II) with phosphorus pentachloride

Chart I



Scheme II



has been developed.[26,27] This method (method A) was adopted in the preparation of several of the amines I (Table I) from the corresponding tertiary allylic alcohols III (Table II) as outlined in Scheme I. The alcohols III were prepared by reaction of vinylmagnesium bromide with the ketones II.[28] The para- and ortho-substituted 3-benzoylpyridines II were prepared by Friedel–Crafts reactions with nicotinoyl chloride. The meta-substituted ketones were obtained via electrophilic substitution (bromination, nitration) of 3-benzoylpyridine itself. Reactions between 4-cyanopyridine and the appropriate phenylmagnesium bromides gave the 4-benzoylpyridines. In order to prepare 2-[4-(dimethylamino)benzoyl]pyridine, a Friedel–Crafts reaction was employed.

The influence of the chlorination reagent on the cis/trans ratio of the amines I formed by the conversion of some representative derivatives III has been investigated (Table III). When X is a strong electron donor, such as alkoxy, the alcohols III (**34** and **39**) are more reactive and can be smoothly chlorinated with anhydrous hydrochloric acid without any Lewis acid, in contrast to the halo-substituted **32** and **33**. Furthermore, the reactive allylic chlorides IV formed from **34**, **39**, and **41** must be aminated directly without washing the crude chlorination mixture with water. As can be seen for **33**, the cis/trans ratios in the product I are increased in the order $PCl_5 > PCl_3 > SOCl_2 > HCl/ZnCl_2$, which is in agreement with previous findings.[29] On the other hand, **34** and **39** exhibit a more uniform behavior upon treatment with different reagents. In such cases (X being an electron donor), the carbonium-like transition state, probably having the pyridine ring out of the allyl plane, is more stabilized and likely to favor the cis orientation irrespective of a cyclic or noncyclic mechanism (Chart I).

In most preparations we used phosphorus pentachloride as reagent, which gave the expected high cis/trans ratios of I after amination. However, the ortho-substituted compounds **36** and **37** gave nearly equal proportions of the

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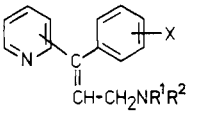
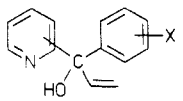
Table I. 3-Aryl-3-pyridylallylamines (I)



no.	py	X	R^1	R^2	isomer[a]	mp (solvent),[b] °C	method[c]	MS (70 eV), *m/z* (rel int)[d]	formula	anal.[e]
1	3	H	Me	Me	cis	152-155 (A)	E	238 (M, 100), 194 (82), 58 (100)	$C_{16}H_{18}N_2 \cdot 1.5C_2H_2O_4$	C, H, N, O
2	3	4-F	Me	Me	cis (90)	151-155 (A)	A	256 (M, 97), 212 (80), 58 (100)	$C_{16}H_{17}FN_2 \cdot C_2H_2O_4$	C, H, F, N
3	3	4-F	H	Me	cis (93)	196-198 (B)	A	242 (M, 100), 212 (32), 44 (45)	$C_{15}H_{15}FN_2 \cdot C_2H_2O_4$	C, H, F, N
4	3	4-Cl	Me	Me	cis (95)	164-168 (A)	A	274/272 (M, 19/55), 193 (33), 58 (100)	$C_{16}H_{17}ClN_2 \cdot C_2H_2O_4$	C, H, Cl, N, O
5	3	4-Cl	H	Me	cis (97)	203-205 (B)	A	260/258 (M, 30/100), 193 (19), 44 (59)	$C_{15}H_{15}ClN_2 \cdot C_2H_2O_4$	C, H, Cl, N, O
6	3	4-Br	Me	Me	cis	196-199 (A)	A[f]	318/316 (M, 29/29), 193 (61), 58 (100)	$C_{16}H_{17}BrN_2 \cdot 2HCl \cdot H_2O$	C, H, Cl, N, O
7	3	4-Br	H	Me	cis	212-214 (B)	A[g]	304/302 (M, 94/100), 193 (58), 147 (72),[h] 44 (84)	$C_{15}H_{15}BrN_2 \cdot C_2H_2O_4$	
8	3	4-Br	H	Et	cis	206-208 (B)	A[g]	318/316 (M, 63/67), 193 (100), 58 (54)	$C_{16}H_{17}BrN_2 \cdot C_2H_2O_4$	
9	3	4-Br	H	Pr	cis	200-202 (B)	A[g]	332/330 (M, 29/30), 193 (100), 72 (9)	$C_{17}H_{19}BrN_2 \cdot C_2H_2O_4$	
10	3	4-Br	Me	Me	trans	174-176	*i*		$C_{16}H_{17}BrN_2 \cdot 1.5C_2H_2O_4$	
11	3	4-Br	H	Me	trans	198-201	*i*		$C_{15}H_{15}BrN_2 \cdot C_2H_2O_4$	
12	3	4-I	Me	Me	cis	170-173 (C)	E	364 (M, 100), 193 (80), 58 (78)	$C_{16}H_{17}IN_2 \cdot C_2H_2O_4$	C, H, I, N, O
13	3	4-CF_3	Me	Me	cis (72)	146-148 (A)	C	306 (M, 81), 262 (45), 58 (100)	$C_{17}H_{17}F_3N_2 \cdot C_2H_2O_4$	H, F; C[j]
14	3	4-Me	Me	Me	cis	183-185 (A)	E	252 (M, 100), 208 (86), 58 (91)	$C_{17}H_{20}N_2 \cdot C_2H_2O_4$	C, H, N, O
15	3	4-$SiMe_3$	Me	Me	cis	185-186 (A)	E	310 (M, 80), 266 (21), 73 (100),[k] 58 (64)	$C_{19}H_{26}N_2Si \cdot C_2H_2O_4$	C, H, N
16	3	4-OMe	Me	Me	cis (98)	175-177 (B)	A	268 (M, 100), 224 (96), 58 (73)	$C_{17}H_{20}N_2O \cdot C_2H_2O_4$	C, H, N, O
17	3	4-SMe	Me	Me	cis	162-164 (D)	E	284 (M, 100), 193 (66), 58 (80)	$C_{17}H_{20}N_2S \cdot C_2H_2O_4$	C, H, N, O, S
18	3	4-CN	Me	Me	cis	152-155 (C)	D	263 (M, 52), 219 (39), 58 (100)	$C_{17}H_{17}N_3 \cdot 1.25C_2H_2O_4$	C, H, N, O
19	3	3-F	Me	Me	cis (75)	159-162 (C)	C	256 (M, 45), 212 (33), 58 (100)	$C_{16}H_{17}FN_2 \cdot C_2H_2O_4$	C, H, F, N
20	3	3-Cl	Me	Me	cis	171-174 (A)	B	274/272 (M, 23/68), 193 (40), 58 (100)	$C_{16}H_{17}ClN_2 \cdot C_2H_2O_4$	C, H, Cl, N, O
21	3	3-Br	Me	Me	cis	162-163 (C)	C	318/316 (M, 65/68), 193 (62), 58 (100)	$C_{16}H_{17}BrN_2 \cdot C_2H_2O_4$	C, H, Br, N, O
22	3	3-Br	H	Me	cis	198-199 (B)	A	304/302 (M, 93/98), 193 (51), 147 (100),[h] 44 (95)	$C_{15}H_{15}BrN_2 \cdot C_2H_2O_4$	C, H, Br, N, O
23	3	2-Br	Me	Me	cis	148-149 (A)	A	318/316 (M, 7/8), 237 (100),[i] 58 (94)	$C_{16}H_{17}BrN_2 \cdot C_2H_2O_4$	C, H, Br, N, O
24	3	2-Br	H	Me	cis	200-202 (B)	A	304/302 (M, 3/4), 223 (100),[i] 44 (76)	$C_{15}H_{15}BrN_2 \cdot C_2H_2O_4$	C, H, Br, N, O
25	3	2,4-Cl_2	Me	Me	cis	167-169 (A)	A	310-306 (M, 3-14), 273/271 (20/59),[i] 58 (100)	$C_{16}H_{16}Cl_2N_2 \cdot C_2H_2O_4$	C, H, Cl, N, O
26	3	2,4-Cl_2	H	Me	cis	203-205 (B)	A	296-292 (M, 3-15), 259/257 (29/100),[i] 44 (63)	$C_{15}H_{14}Cl_2N_2 \cdot C_2H_2O_4$	C, H, Cl, N, O
27	4	4-Cl	Me	Me	cis	189-190 (B)	A	274/272 (M, 27/78), 196/194 (21/71),[m] 58 (100)	$C_{16}H_{17}ClN_2 \cdot C_2H_2O_4$	C, H, Cl, N, O
28	4	4-*i*-PrO	Me	Me	cis	201-203 (B)	A	296 (M, 88), 218 (48),[m] 210 (100),[n] 58 (69)	$C_{19}H_{24}N_2O \cdot C_2H_2O_4$	C, H, N, O
29	4	3-Me	Me	Me	cis	196-198 (B)	A	252 (M, 100), 208 (43), 174 (65),[m] 58 (86)	$C_{17}H_{20}N_2 \cdot 2C_2H_2O_4$	C, H, N, O
30	2	4-NMe_2	Me	Me	cis	165-166 (A)	A	281 (M, 100), 237 (54), 58 (13)	$C_{18}H_{23}N_3 \cdot C_2H_2O_4$	C, H, N, O

[a] Isomeric purity ≥99% unless the approximate percentage is indicated in parentheses. For nomenclature, see ref 24. [b] Oxalate salts except for 6 (dihydrochloride). Recrystallization solvent: A = EtOH; B = EtOH/H_2O; C = EtOH/*i*-Pr_2O; D = EtOH/Et_2O. [c] See Experimental Section for details. A = amination; B = dehydration; C = Wittig; D = substitution; E = lithiation-substitution. [d] The prominent ions M, [M − NR^1R^2] or [M − NR^1R^2 − X], and [CH_2=NR^1R^2] are indicated unless otherwise noted. [e] Elemental analyses are within ±0.4% of the calculated values unless otherwise noted. [f] Prepared in analogy with ref 26. [g] Described in ref 27. [h] [M − C_6H_4Br]. [i] Described in ref 25. [j] C: calcd, 57.58; found, 58.08. [k] [$SiMe_3$]. [l] Ortho-substituted compound having pronounced [M − X]. [m] 4-Pyridyl derivative having pronounced [M − C_5H_4N]. [n] [M − C_3H_6 − NMe_2].

Table II. 1-Aryl-1-pyridyl-2-propen-1-ol (III)[a]



no.	py	X	mp, °C	recrystn solvent	yield,[b] %	formula	anal.[c]
31	3	4-F	80-81	Et_2O-C_5H_{12}	85	$C_{14}H_{12}FNO$	*d*
32	3	4-Cl	82.5-84	PhMe	88	$C_{14}H_{12}ClNO$	*d*
33	3	4-Br	76-77[e]	Et_2O	85	$C_{14}H_{12}BrNO$	*d*
34	3	4-OMe	76-78	Et_2O-C_5H_{12}	88	$C_{15}H_{15}NO_2$	*d*
35	3	3-Br	oil		90	$C_{14}H_{12}BrNO$	*f*
36	3	2-Br	111-112	*i*-Pr_2O	47[g]	$C_{14}H_{12}BrNO$	*d*
37	3	2,4-Cl_2	111-112	*i*-Pr_2O-*i*-PrOH	34[g]	$C_{14}H_{11}Cl_2NO$	C, H, Cl, N, O
38	4	4-Cl	146-148	*i*-Pr_2O-*i*-PrOH	61[g]	$C_{14}H_{12}ClNO$	C, H, Cl, N, O
39	4	4-*i*-PrO	128-129	*i*-Pr_2O-*i*-PrOH	35[g]	$C_{17}H_{19}NO_2$	C, H, N, O
40	4	3-Me	124-126	*i*-Pr_2O-*i*-PrOH	53[g]	$C_{15}H_{15}NO$	C, H, N, O
41	2	4-NMe_2	48-50	*i*-Pr_2O	52[g]	$C_{16}H_{18}N_2O$	C, H, N, O

[a] See Experimental Section for details. [b] Refers to crude yield unless otherwise noted. [c] Elemental analyses are within ±0.4% of the calculated values. [d] See ref 28. [e] Literature[26] mp 68-70 °C. [f] No analytical sample was made. [g] Yield after recrystallization.

Table III. Percentage of the Cis Isomer of the Allylamine I Formed after Chlorination of III and Subsequent Dimethylamination (See Scheme I)

	chlorination reagents[a]					
III	PCl_5	PCl_3	$SOCl_2$	HCl	HCl/$ZnCl_2$	product I
32	87			No[b]	50	4
33	86	71	60[c]	No[b,d]	50	6
34	77	77	73	64		16
36	46		58[e]			23
39	86		81	84		28

[a] The alcohols III were treated with 1.5-2 equiv of halide in CH_2Cl_2 during 3 h at room temperature and then with excess of $HNMe_2$ in CH_2Cl_2. After addition of 2 M NaOH, the organic layer was analyzed on a gas chromatograph equipped with an electronic integrator assuming identical response factors (OV-1 capillary column 205 °C). A complete conversion to I was observed unless otherwise noted. [b] No conversion (<0.5%) took place with anhydrous HCl. [c] A conversion of 94%. [d] Reaction in concentrated aqueous HCl gave complete conversion (60% cis). [e] A conversion of 62%.

two isomers (cf. data for **36** in Table III). Hydrogen chloride was used in the case of **34** and **39**, and thionyl chloride was used for **41**. Direct amination of the crude allylic chloride III accomplished the transformations to **16**, **28**, and **30** satisfactorily. Recently, an alternative way of converting the tertiary allylic alcohols by a palladium-catalyzed amination of the corresponding acetate has been described.[28]

The compound **20** was prepared as shown in Scheme II (method B). The dehydrated crude product had a cis/trans ratio of about 5:2, and the pure cis form was obtained by recrystallization.

An alternative way to the tertiary amines, using the benzoylpyridines II, is the direct Wittig procedure shown in Scheme I (method C). The reaction with the ylide was performed in tetrahydrofuran, and the amines **13**, **19**, and **21** were produced in ~90% yield with cis/trans ratios of about 3:2. The 3-bromo derivative (**21**) could be isolated as the desired cis form by recrystallization, whereas **13** (4-CF_3) and **19** (3-F) were tested as cis/trans mixtures (ca. 3:1).

Another quite different approach of preparing 4-substituted zimelidine analogues utilizes the ready availability of zimelidine (**6**) in our laboratories. Copper-promoted nucleophilic substitutions of bromide were attempted with methoxide, ethyl mercaptide, and cyanide anions, but the only successful substitution was with cyanide leading to **18** (method D, Table I). The crude product contained about 16% unreacted **6** and it proved difficult to get complete conversion without increasing the amounts of side-products. However, it was possible to separate **6** and **18** due to their different lipophilicities. Thus, repeated extractions of a water phase (pH 6.1-6.2) with ether enriched the cyano compound **18** in the aqueous layer without unreasonable losses.

Alternatively, **6** was converted to the corresponding lithio compound by halogen–metal exchange with butyllithium at low temperature. Interestingly, it was observed that methyllithium did not accomplish the same exchange (cf. ref 30). A similar difference between butyllithium and methyllithium has been observed for the cleavage of the carbon–selenium bond in some selenoacetals.[31] The lithio derivative formed from **6** was reacted with various electrophiles, such as water, hexachloroethane, iodine, methyl iodide, trimethylsilyl chloride, and dimethyl disulfide, which led to the compounds **1**, **4**, **12**, **14**, **15**, and **17**, respectively (method E, Table I). The synthesis of **4** was carried out only for analytical purposes. The cis configuration was retained during these transformations as shown by UV and NMR.

Configurational Assignments.[24] The structure of zimelidine (**6**) has been established by X-ray single-crystal analysis.[22] Later it was shown that the configuration of tertiary 3- and 4-pyridylallylamines could be determined by lanthanide-induced shifts (LIS) in ^1H NMR.[23,28] Furthermore, UV spectra have been used to correlate metabolites and secondary amine analogues to zimelidine.[20,27] In this paper we have combined these approaches and also taken advantage of the fact that the compounds **1**, **4**, **12**, **14**, **15**, **17**, and **18** are derived directly from zimelidine in a stereospecific way by the exchange methods D and E. In Table IV the UV data in 0.1 M hydrochloric acid and the relevant LIS parameters are shown.

The LIS were obtained with $Eu(fod)_3$ in $CDCl_3$. Table IV shows the gradient (slope of shift diagrams) ratios *G* (2-pyridine)/*G* (NMe_2) and *G* (allyl)/*G* (vinyl) according to our previous description.[23] As can be seen from the values of *G* (2-pyridine)/*G* (NMe_2), the Eu atom is complexed preferentially to the pyridine nitrogen. Thus, the *G* (allyl)/*G* (vinyl) ratios larger than 1 are consistent with

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Table IV. Configurational Assignments of the Amines I by UV Spectra and Lanthanide-Induced Shifts (LIS) in ^{1}H NMR

no.	UV (0.1 M HCl) λ_{max} (ϵ)	UV (0.1 M HCl) λ_{min} (ϵ)	LIS[a] G (allyl)/G (vinyl)	LIS[a] G (2-py)/G (NMe_2)	confign
1	238 (13 500)	220 (10 600)			cis[b]
2	239 (13 900)	223 (12 100)	1.5	10	cis
3	239 (14 500)	222 (12 000)			cis
4	246 (17 600)	224 (12 400)	1.5	8.8	cis
5	245 (18 500)	224 (13 300)			cis
6	250 (19 700)	225 (14 000)	1.5	9.6	cis
10	219 (21 900)		0.39	17	trans
12	256 (20 000)	229 (12 600)			cis[b]
13			1.6	12	cis
			0.35	21	trans
14	246 (16 200)	225 (11 400)			cis[b]
15	246 (18 800)	223 (12 100)			cis[b]
16	255 (16 900)	231 (10 300)	1.5	7.9	cis
17	288 (14 300)	246 (10 100)			cis[b]
18	260 (23 700)	223 (13 400)			cis[b]
19			1.5		cis
			0.46		trans
20	235 (16 000)	225 (15 100)	1.6	12	cis
21	235 (18 000)[c]		1.6	13	cis
22	236 (16 700)[c]				cis
23	261 (5 300)[c]		1.5	11	cis
24	262 (5 000)[c]				cis
25	260 (8 000)[c]		1.5	11	cis
26	260 (8 500)[c]				cis
27	252 (20 900)	221 (9 700)	1.3	12	cis
28	261 (20 300)	227 (8 500)	1.3	11	cis
29	248 (15 900)	228 (12 800)	1.4	12	cis
30[d]	285 (15 600)	248 (9 300)	2.0	0.33	cis

[a] LIS determined after incremental addition of solid $Eu(fod)_3$ to the amine I (base) dissolved in $CDCl_3$. The gradient (G) refers to the slope of shift diagrams. For further details, see ref 23. [b] Synthesized from 6 (cis) by exchange of Br with retained configuration. [c] Shoulder. [d] UV for oxalate salt in ethanol.

isomers having the pyridine ring and the allylamine oriented in a cis fashion.[23,24]

Presuming binding of Eu to the pyridine nitrogen, 2-pyridyl derivatives cannot be assigned by LIS in the same way as for the 3- and 4-pyridyl compounds, since the allylic and vinylic protons would occupy shielding as well as deshielding regions in the complex.[23] The G (2-pyridine)/G (NMe_2) ratio for **30** may indicate a bidentate complex, which is likely only for the cis isomer (cf. ref 28). Besides, the vinyl proton in the trans form of *N,N*-dimethyl-3-phenyl-3-(2-pyridyl)allylamine has an extreme downfield ^{1}H NMR shift (6.95 ppm for trans and 6.28 ppm for cis),[28] which confirms the cis configuration for **30** having a vinyl shift of 6.15 ppm.

In addition, the 3-pyridyl derivatives exhibit different relative shifts of the 2- and 6-pyridyl protons for the cis and trans isomers.[20,23,25] The 6-pyridyl double doublet is downfield in the cis forms of all derivatives studied so far except when the phenyl ring is ortho substituted (**23–26**).

The UV spectra support the above proofs and provide the complementary stereochemical information. In most cases the UV spectrum itself establishes the configuration, since the cis and trans forms have quite different spectra.[20,32,33] This can be seen for the compounds **6** and **10** having known structures (Table IV). The cis isomers are likely to have the phenyl ring relatively coplanar with the olefin, whereas the protonated and sterically more hindered pyridine ring is out of the olefin plane.[22,33] Accordingly, the 3-pyridyl series **1**, **2** and **3**, **4** and **5**, **14**, **15**, **6**, **16**, **12**, **18**, and **17** exhibit substituent effects analogous to that found, for example, for benzoyl chromophores.[34]

Also, the 4-pyridyl derivatives **27–29** and the 2-pyridyl derivative **30** (cf. UV of **17**) can be assigned as cis isomers. The meta-halogenated derivatives **20–22** are also likely to have the cis form according to UV (cf. LIS data). However, the ortho-substituted phenyl rings in **23–26** are probably forced out of conjugation with the olefin, and the UV spectra give no reliable indication of the steric relationships. As mentioned above, the tertiary amines **23** and **25** had the cis configuration according to the LIS investigation, and thus the secondary amines **24** and **26** also could be assigned as cis forms due to the resemblance of their UV spectra.

Structure–Activity Relationships

Inhibition of NA and 5-HT Accumulation. The accumulation of ^{3}H-labeled NA and ^{14}C-labeled 5-HT was determined on slices from the middle part of the mouse brain (male albino, NMRI) as described previously.[7] The inhibition of the accumulation was determined in percent of control, and the IC_{50} and ED_{50} values were estimated from semilogarithmic plots (Table V).

Amine Substitution. Previous investigations showed the secondary amine norzimielidine (**7**) to be a more potent uptake inhibitor than zimelidine (**6**) in the rat brain.[21] The same result was found in the mouse (Table V). The secondary amines **8** and **9** with larger *N*-alkyl groups (ethyl and propyl) were markedly less active than **7**. The in vitro activity of **8** was the same as that of **6**. However, **8** was devoid of 5-HT activity in vivo in contrast to **6**, which has part of its effect mediated by the metabolite **7**. In fact, the uptake inhibition after administration of zimelidine was correlated to the concentration of **7** rather than **6** in the rat brain.[21,35] Generally, the secondary *N*-methyl

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Table V. Inhibition of the Accumulation of (−)-[^{3}H]Noradrenaline (NA) and 5-Hydroxy[^{14}C]tryptamine (5-HT) in Mouse Brain Slices[a]

compd[b]	in vitro IC_{50}, μM		in vivo ED_{50}, μmol/kg ip	
	NA	5-HT	NA	5-HT
1	27	3.7	>107 (37%)[c]	>107 (23%)[c]
2	29	4.0	79	115
3	1.5	1.4	42	120
4	10	2.1	38	36
5	1.1	0.2	49	24
5[d]	0.12	0.5	5.2	46
6[e]	24	1.7	>98 (26%)	49
7	1.5	0.10	>102 (38%)	19
8	26	2.0	>102 (1%)	>102 (44%)
9	>24 (42%)	24	>95 (30%)	>95 (34%)
10	6.1	6.1	25	>98 (36%)
11	0.8	2.5	25	102
12	>22 (33%)	1.0	>88 (−8%)	41
13	13	2.0	>101 (17%)	107
14	>29 (41%)	2.4	>117 (12%)	>117 (28%)
15	>25 (25%)	25	>100 (−7%)	>100 (−20%)
16	>28 (37%)	0.8	>112 (40%)	>112 (43%)
17	>27 (24%)	0.5	>107 (−11%)	107
18	>28 (24%)	7.4	>113 (−4%)	>113 (25%)
19	2.2	1.6	33	>115 (33%)
20	11	2.6	>110 (41%)	>110 (12%)
21	4.2	0.9	66	>98 (26%)
22	0.9	1.4	58	>102 (23%)
23	2.2	4.2	37	>98 (43%)
24	0.3	0.6	20	102
25	11	1.5	>101 (31%)	43
26	2.3	0.5	73	18
27	>27 (25%)	3.0	108	33
28	34	3.5	>135 (−9%)	>135 (−3%)
29	14	8.8	>93 (−12%)	>93 (−7%)
30	11	1.6	>108 (37%)	>108 (35%)
alaproclate[f]	>34 (14%)	0.7	>137 (0%)	51
brompheniramine	4.7	0.3	63	13
chlorimipramine	0.9	0.09	142	20
desipramine	0.07	12	34	>132 (30%)
imipramine	1.3	0.3	63	126

[a] See Experimental Section for details. [b] The oxalates described in Table I were used unless otherwise noted. [c] The values in parentheses indicate the inhibition at the highest dose level in percent. [d] A cis/trans mixture (17:83) of base isolated by preparative HPLC. [e] Hydrochloride. [f] Reference 10.

derivatives were more active on 5-HT as well as NA than the corresponding tertiary amines (Table V). The biotransformation to the secondary amines may explain the observation that many tertiary amines were more active in vivo than one should expect from the in vitro data.

The selectivity of the 5-HT uptake inhibition was the same for **6**, **7**, and **8**; i.e., they were tenfold more active on 5-HT than on NA. This is in contrast to the behavior of many tricyclics, e.g., imipramine and desipramine (Table V).[2,12]

Phenyl Substitution. Comparison of the bromo derivatives **6**, **21**, and **23** and **7**, **22**, and **24** revealed a decrease in 5-HT activity and an increase in NA activity in the order 4-Br, 3-Br, 2-Br. As mentioned earlier, the conformation of ortho-substituted compounds differs from that of other cis derivatives due to the twisting of the phenyl ring out of the olefin plane as shown by UV. This lack of coplanarity between the phenyl and olefin might partly explain the similarity in NA activity of **23** and **24** and **10** and **11**. The latter pair with the trans configuration is also likely to have the phenyl ring out of plane.

The influence of the electronic, lipophilic, and steric nature of the para-phenyl substituent X on 5-HT uptake was examined. The in vitro effect on 5-HT was rather insensitive to variations in X. Only the very large $SiMe_3$ group (**15**), the hydrophilic CN group (**18**), and to some extent the small F (**2**) and H (**1**) substituents resulted in loss of the 5-HT activity. However, only strong in vivo activity on 5-HT was found with the larger halogens Cl (**4**), Br (**6**), and I (**12**). All the para-substituted tertiary cis compounds lacked NA activity in vivo, except **2** and **4**, the effect of which might partly be explained by contamination with trans isomers, which could also be biotransformed to the more potent secondary amines. Note that the trans isomers **10** and **11** were equipotent in vivo on NA, but **11** was tenfold more active in vitro. In order to test this assumption, the trans form of **5** was enriched (83%) and investigated. The effect on NA was substantial also in comparison with **11** (Table V).

The 3-Cl derivative **20** had decreased NA activity in comparison to 3-Br (**21**). The NA effect of **19** (3-F) is likely due to the high content of trans isomer in the substance.

A combination of the substitution patterns in the cis derivatives favoring 5-HT (para) and NA (ortho) was made in the 2,4-Cl_2 compounds **25** and **26**. The compounds showed a pronounced 5-HT activity, and the secondary amine **26** a certain NA activity.

Miscellaneous Pyridines. Some 2- and 4-pyridyl derivatives were investigated. In two compounds (**28** and **30**), strong electron donors (4-*i*-PrO and 4-NMe_2) were combined with the 4- and 2-pyridine systems, respectively, in order to reinforce the possibility of cross-conjugation. However, this approach apparently gave no active compounds. The 4-Cl compound **27** showed a fairly selective 5-HT uptake inhibition.

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Experimental Section

Chemistry. Melting points were determined on a Mettler FP 61 apparatus in open capillary tubes and are uncorrected. ^1H NMR spectra were recorded on a Varian T-60 spectrometer, and the spectra are consistent with the proposed structures. The chemical shifts are reported in δ (ppm) units relative to internal Me_4Si. UV spectra were obtained on a Zeiss DMR 21 spectrophotometer (see Table IV). Mass spectra (70 eV) were recorded on an LKB 9000 instrument (see Table I). GC were run on a JXR or OV-17 column or an OV-1 capillary column. HPLC were conducted on a reversed-phase system (Nucleosil 5μ; acetonitrile/phosphate buffer, pH 3.0, 15:85) with UV detection at 254 nm. TLC were run on precoated plates (Merck, silica gel F_{254}). Elemental analyses, performed by Analytische Laboratorien, Elbach, West Germany, were within ±0.4% of the theoretical values unless otherwise noted. See also Tables I and II for physical data and ref 28 for ^1H NMR for some of the alcohols III and amines I.

Benzoylpyridines (II). 3-(Substituted-benzoyl)pyridines with X = 4-Br, 4-Cl, 4-F, 2-Br, and 4-OMe were prepared by Friedel–Crafts reactions from nicotinoyl chloride as described recently,[28] with X = 2,4-Cl_2 similarly according to Sauter et al.,[36] and with X = 4-CF_3 according to DoAmaral et al.[37]

3-(3-Bromobenzoyl)pyridine. To a mixture of 3-benzoylpyridine (18.3 g, 0.10 mol) and anhydrous $AlCl_3$ (33.3 g, 0.25 mol) was added Br_2 (19.2 g, 0.12 mol) at 80–100 °C during 20 min. The mixture was heated at 80 °C with stirring for 4 h and then poured into a mixture of 200 g of ice and 20 mL of concentrated HCl. The acid solution was made alkaline and extracted three times with ether. The organic phase was dried ($MgSO_4$) and evaporated. The pure product was obtained after two recrystallizations from ethanol in 30% yield: mp 64–65 °C; ^1H NMR ($CDCl_3$) δ 7.2–8.1 (m, 5, aromatic), 8.11 (dt, 1, 4-pyridyl), 8.83 (dd, 1, 6-pyridyl), 9.00 (m, 1, 2-pyridyl). Anal. ($C_{12}H_8BrNO$) C, H, Br, N, O.

3-(3-Nitrobenzoyl)pyridine was prepared by nitration of 3-benzoylpyridine in analogy with the method of Hands and Katritsky for 2-(3-nitrobenzoyl)pyridine:[38] yield 66%; mp 76–78 °C. Anal. ($C_{12}H_8N_2O_3$) C, H, N, O.

3-(3-Aminobenzoyl)pyridine was prepared by reduction of 3-(3-nitrobenzoyl)pyridine with $SnCl_2$/HCl in analogy with the method of Sauter et al. for 4-(3-aminobenzoyl)pyridine:[36] yield 66%; mp 93–95 °C. Anal. ($C_{12}H_{10}N_2O$) C, H, N, O.

3-(3-Fluorobenzoyl)pyridine. To a solution of 3-(3-aminobenzoyl)pyridine (15.4 g, 78 mmol) in 150 mL of tetrahydrofuran (THF) was added 126 g of 35% HBF_4 at about −10 °C. $NaNO_2$ (5.6 g, 82 mmol) dissolved in 10 mL of water was added at −10 °C in 20 min. After 0.5 h, the precipitate was filtered off and washed with 5% HBF_4, methanol, and ether. The crude diazonium salt was heated in a flask with an open flame until the evolution of gas had ceased (about 15 min). The residue was taken up in water and ether and made alkaline. The organic phase was treated with charcoal, dried ($MgSO_4$), and evaporated to yield 80% of pure base (GC). An analytical sample of the hydrochloride was prepared and recrystallized from ethanol: mp 192–195 °C; ^1H NMR (base, $CDCl_3$) δ 7.2–7.7 (m, 5, aromatic), 8.07 (dt, 1, 4-pyridyl), 8.77 (dd, 1, 6-pyridyl), 8.93 (m, 1, 2-pyridyl). Anal. ($C_{12}H_8FNO$·HCl) C, H, Cl, F, N.

4-(4-Isopropoxybenzoyl)pyridine. 1-Bromo-4-isopropoxybenzene (62.3 g, 0.26 mol) dissolved in 100 mL of dry ether was added to Mg (6.9 g, 0.28 mol) in 20 mL of ether during 1 h. The mixture was stirred at ambient temperature for 2 h. The Grignard solution was added dropwise to 4-cyanopyridine (29.9 g, 0.29 mol) in 100 mL of ether during 2 h. After the mixture was stirred for 1 h, 200 mL of dry toluene was added, and the mixture was stirred for 2 days at about 70 °C. After the mixture was hydrolyzed with 200 mL of 2 M HCl and separated, the aqueous layer was made alkaline and extracted with ether. The ether phase was dried ($MgSO_4$) and evaporated. The residue was recrystallized from diisopropyl ether/hexane to give 24.9 g (36%) of pure ketone: mp 50–52 °C; ^1H NMR ($CDCl_3$) δ 1.38 (d, 6, CH_3), 4.70 (m, 1, CH), 6.95 (AA′, 2, 3,5-phenyl), 7.52 (CC′, 2, 3,5-pyridyl), 7.80 (BB′, 2, 2,6-phenyl), 8.77 (DD′, 2, 2,6-pyridyl). Anal. ($C_{15}H_{15}NO_2$) C, H, N, O. The following two compounds were similarly prepared.

4-(4-Chlorobenzoyl)pyridine was obtained from 4-cyanopyridine and 4-chlorophenylmagnesium bromide after heating at 80 °C for 1.5 h in toluene: yield 60%; mp 109–110 °C (lit.[39] mp 108–109 °C, Friedel–Crafts reaction).

4-(3-Methylbenzoyl)pyridine was obtained from 4-cyanopyridine and 3-methylphenylmagnesium bromide after heating at 70 °C for 4 h in toluene: yield 51%; mp 54–56 °C. Anal. ($C_{13}H_{11}NO$) C, H, N, O. Compare ref 40.

2-[4-(Dimethylamino)benzoyl]pyridine. A mixture of picolinic acid (73.8 g, 0.60 mol) and 600 mL of $SOCl_2$ was refluxed for 2 h. Excess $SOCl_2$ was removed in vacuo. The residue was suspended in 500 mL of ether, and the slurry was added to $AlCl_3$ (240 g, 1.8 mol) in 1 L of ether at 10–15 °C. Dimethylaniline (182 g, 1.5 mol) was added at 10–20 °C in 40 min, and the mixture was refluxed for 1 h. After cooling, the mixture was added to 700 mL of 45% NaOH in 1 L of ice–water. The phases were separated, and the organic phase was partly evaporated. The precipitate in the residue was filtered off, washed with ether, and recrystallized from ethanol: yield 58%; mp 91–93 °C; ^1H NMR ($CDCl_3$) δ 3.03 (s, 6, CH_3), 6.67 (AA′, 2, 3,5-phenyl), 7.4 (m, 1, 5-pyridyl), 7.9 (m, 2, 3,4-pyridyl), 8.09 (BB′, 2, 2,6-phenyl), 8.70 (dm, 1, 6-pyridyl). Anal. ($C_{14}H_{14}N_2O$) C, H, N, O.

Method A (General Procedures). 1-Aryl-1-pyridyl-2-propen-1-ol (III: 31–41). A solution of vinyl bromide (13.4 g, 125 mmol) in 40 mL of dry THF was added to Mg (3.2 g, 130 mmol) in 10 mL of THF under N_2 at about 60 °C. After the mixture was refluxed for 1 h, the Grignard reagent was added to the benzoylpyridine II (100 mmol) in 80 mL of THF at 10 to 20 °C. After the mixture was stirred at ambient temperature for 2 h, a solution of 6 g of NH_4Cl in 30 mL of water was added with ice cooling. The mixture was filtered, and the organic phase was evaporated. The residue was taken up in ether, treated with charcoal, and dried ($MgSO_4$). After filtration the solvent was evaporated to give an oil, which in certain cases (36–41) solidified and was purified by recrystallization. The results are shown in Table II.

1-Aryl-3-chloro-1-pyridyl-1-propene (IV). A solution of 40 mmol of crude or pure III (31–33, 35–38, and 40) in 100 mL of CH_2Cl_2 was added dropwise to a suspension of PCl_5 (60 mmol) in 20 mL of CH_2Cl_2 during 0.5 h at ~10 °C. After stirring for 1 h at room temperature, the solution was washed with 50 mL of water at 0 to 10 °C. The solution of the crude IV was used directly in the following aminations.

In the case of compounds 34 and 39, 24 mmol of HCl in ether was added to the alcohol (10 mmol) in 30 mL of CH_2Cl_2 at ambient temperature. The solution was stirred for 0.5 h, and the crude allylic chloride solution was aminated directly without washing with water. Compound 41 (2.5 g, 10 mmol) in 25 mL of CH_2Cl_2 was added to $SOCl_2$ (2.4 g, 20 mmol) in 20 mL of CH_2Cl_2, and the solution was stirred for 0.5 h. The solution of crude product was aminated directly without washing.

3-Aryl-*N*,*N*-dimethyl-3-pyridylallylamine (I: 2, 4, 6, 16, 23, 25, 27, and 30). A solution of crude IV (20 mmol) was added to dimethylamine (9.0 g, 200 mmol) in 15 mL of CH_2Cl_2 at about 10 °C. After the mixture was stirred at room temperature for 1 h, 20 mL of water was added, and the phases were separated. The organic layer was evaporated, and the residue was taken up in ether and extracted with HCl at pH ~4.5. The aqueous phase was made alkaline and extracted with ether. Drying ($MgSO_4$) and evaporation of the ether gave I as a residual oil in 60–70% crude yield. The cis isomer was enriched by precipitation from acetone or ethanol with oxalic acid (about equimolar to the amount of cis isomer) and recrystallization from the solvent indicated in Table I in a yield of 35–50%.

3-Aryl-*N*-methyl-3-pyridylallylamine (I: 3, 5, 22, 24, 26). A solution of crude IV was reacted with methylamine in ethanol

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in analogy with the above procedure. (It was found advantageous to use ethanol as cosolvent in this case.) The side-product formed by dialkylation was efficiently removed by the ether extraction at pH ~4.5. The crude yield of I was 40–50%, and the cis isomer was isolated in 20–30% yield.

Method B (20). 2-(3-Chlorobenzoyl)-*N*,*N*-dimethylethylamine (42). 3-Chloroacetophenone (35.8 g, 0.23 mol), dimethylamine hydrochloride (28.1 g, 0.35 mol), paraformaldehyde (13.8 g, 0.46 mol), and 0.75 mL of concentrated HCl were refluxed in 60 mL of ethanol for 5 h. After the solution cooled, the precipitated hydrochloride was collected and dried in vacuo: yield 42.3 g (86%); mp 189–191 °C. Recrystallization form ethanol/water (15:1) gave the pure hydrochloride: mp 193–195 °C. Anal. ($C_{11}H_{14}ClNO$·HCl) C, H, Cl, N, O.

3-(3-Chlorophenyl)-3-hydroxy-*N*,*N*-dimethyl-3-(3-pyridyl)propylamine (43). 3-Bromopyridine (15.2 g, 96 mmol) was added to 61 mL of a hexane solution of butyllithium (92 mmol) in 25 mL of ether at about −50 °C during 40 min. After the solution was stirred for 15 min, **42** (base, 16.9 g, 80 mmol) in 25 mL of ether was added at about −50 °C during 1 h. After stirring at −40 to −50 °C for 2 h, the mixture was poured into 120 mL of water and 14 mL of concentrated HCl. The pH was adjusted to about 6, and the solution was extracted with petroleum ether (80–110 °C). The aqueous phase was made alkaline and extracted with ether. The ether phase was dried ($MgSO_4$) and evaporated to yield 21.4 g of a brown oil, which crystallized. The solid was triturated with petroleum ether (80–110 °C) and then recrystallized from petroleum ether (80–110 °C) to give 9.6 g (41%) of white crystals, mp 102–104 °C. Anal. ($C_{16}H_{19}ClN_2O$) C, H, Cl, N, O.

(*Z*)-3-(3-Chlorophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine Oxalate (20). A solution of **43** (4.45 g, 15 mmol) in 5 mL of glacial acetic acid and 3.3 mL of concentrated H_2SO_4 was refluxed for 1 h. After the solution was cooled, 25 mL of water and concentrated NH_3 were added to pH 9.5, and the mixture was extracted with ether. The ether phase was dried ($MgSO_4$) and evaporated to yield 3.6 g (88%) of a brown oil (*Z*/*E* isomeric ratio 72:28 according to GC). The base mixture was dissolved in 20 mL of acetone, and 1 equiv of oxalic acid in acetone was added to precipitate **20**, which was recrystallized from ethanol to give a white crystalline substance (<0.5% *E* isomer): mp 171–174 °C; ^1H NMR (base, $CDCl_3$) δ 2.20 (s, 6, CH_3), 2.95 (d, 2, allyl), 6.28 (t, 1, vinyl), 7.0–7.6 (m, 6, aromatic), 8.40 (m, 1, 2-pyridyl), 8.55 (dd, 1, 6-pyridyl).

Method C (13, 19, and 21). (*Z*)-3-(3-Bromophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine Oxalate (21). Butyllithium in hexane (10.5 mmol) was injected into a mixture of [(dimethylamino)ethyl]triphenylphosphonium bromide (4.34 g, 10.5 mmol) in 25 mL of dry THF at ambient temperature under N_2. After the mixture was stirred for 15 min, a solution of 3-(3-bromobenzoyl)pyridine (2.62 g, 10 mmol) in 20 mL of THF was injected into the solution of dark red ylide. The mixture was heated to 60 °C and stirred overnight. After the mixture was cooled and 75 mL of 2 M HCl was added, the solution was extracted with 100 mL of toluene. The organic layer was extracted with 20 mL of 2 M HCl. The combined aqueous phases were washed with 3 × 50 mL of toluene, made alkaline, and extracted twice with ether. Drying ($MgSO_4$) and evaporation of the ether phase afforded 2.9 g (91%) of the base as a yellow oil. The *Z*/*E* isomeric ratio was found to be 53:47 according to $Eu(fod)_3$ shifted ^1H NMR.[23]

The base mixture (2.7 g, 8.5 mmol) was dissolved in hot acetone, and 0.9 mL of concentrated HCl was added. The mixture was cooled and the acetone was decanted from the semisolid precipitate, which consisted of 1.7 mmol of the pure *Z* form according to GC and NMR. The product was converted to base and then oxalate, which was recrystallized from ethanol/diisopropyl ether to give 0.53 g (1.3 mmol) of **21**: mp 162–163 °C; ^1H NMR (base, $CDCl_3$) δ 2.20 (s, 6, CH_3), 2.97 (d, 2, allyl), 6.32 (t, 1, vinyl), 7.1–7.7 (m, 6, aromatic), 8.51 (m, 1, 2-pyridyl), 8.61 (dd, 1, 6-pyridyl).

The amines **13** (4-CF_3) and **19** (3-F) were prepared analogously (Table I). However, the *Z* forms could only partially be enriched by fractional recrystallization (*Z*/*E* ≈ 3:1).

Method D. (*Z*)-3-(4-Cyanophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine Oxalate (18). Zimelidine (**6**, base, 6.34 g, 20 mmol) and CuCN (2.68 g, 30 mmol) were stirred in 25 mL of dry dimethylformamide at 150 °C for 16 h. After the mixture was cooled and 2 M NaOH was added, the mixture was extracted with ether and filtered through Celite. The ether layer was washed several times with water, dried ($MgSO_4$), and evaporated to give 1.7 g, containing 83% **18** and 16% unreacted **6** (GC). The mixture was dissolved in HCl at pH 6.1–6.2 and extracted seven times with ether. (The pH was optimized in a preceding GC study of extraction at different pH values, and it was found that approximately twice as much **6** as **18** was dissolved in the ether layer at this pH.) After each extraction the pH had to be adjusted with HCl. Finally, the aqueous layer was made alkaline, extracted with ether, dried ($MgSO_4$), and evaporated to afford 1.0 g (19%) of the crystalline base containing only 1% **6**. Conversion to oxalate and recrystallization from ethanol/diisopropyl ether gave 1.0 g of **18**: mp 152–155 °C; ^1H NMR (base, $CDCl_3$) δ 2.23 (s, 6, CH_3), 3.00 (d, 2, allyl), 6.53 (t, 1, vinyl), 7.32 and 7.57 (AA′BB′, 2, C_6H_4), 7.3–7.7 [m (concealed), 2, 4,5-pyridyl], 8.43 (m, 1, 2-pyridyl), 8.60 (dd, 1, 6-pyridyl).

Method E (1, 12, 14, 15, and 17). (*Z*)-3-(4-Iodophenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine Oxalate (12). Butyllithium (10 mmol) in 10 mL of hexane was injected through a septum to a stirred solution of zimelidine (**6**, base, 3.2 g, 10 mmol) in 30 mL of dry THF under N_2 at −65 °C. The deep red solution was stirred for 0.5 h at −65 °C and then I_2 (2.54 g, 10 mmol) was added. The mixture was stirred for an additional 0.5 h at −65 °C and then allowed to reach room temperature during 1.5 h. Water was added, THF was evaporated, and the residue was extracted with ether. The ether phase was washed with $NaHSO_3$, dried ($MgSO_4$), and evaporated to give 2.7 g of an oil. This residue was dissolved in HCl at pH 5.9 and extracted with 1,2-dichloroethane. The organic phase was evaporated to give a residue of 1.8 g, which was triturated three times with ether, leaving 1.0 g of the off-white crystalline hydrochloride. This product was converted to the base (0.7 g, 20%) and crystallized as the oxalate from ethanol/diisopropyl ether: mp 170–173 °C; ^1H NMR (base, $CDCl_3$) δ 2.21 (s, 6, CH_3), 2.98 (d, 2, allyl), 6.32 (t, 1, vinyl), 6.97 (AA′, 2, 2,6-phenyl), 7.63 (BB′, 2, 3,5-phenyl) 7.2–7.8 [m (concealed), 2, 4,5-pyridyl], 8.47 (m, 1, 2-pyridyl), 8.58 (dd, 1, 6-pyridyl). The following four compounds were prepared in a similar way.

(*Z*)-3-[4-(Methylthio)phenyl]-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine Oxalate (17). Zimelidine (**6**, 20 mmol) was lithiated as described above (**12**) and reacted with 25 mmol of dimethyl disulfide at −65 °C. Probably due to contamination of the disulfide with thiol, the crude product contained ~30% of hydrolyzed product (**1**). After evaporation of THF, ether was added and the ether phase was washed four times with an aqueous solution having pH 7.2. (The pH was optimized in a preceding GC study of extraction at various pH values.) The resulting ether layer containing 10% **6** was dried ($MgSO_4$) and evaporated to afford 1.45 g of an oil. Precipitation as oxalate and recrystallizations from ethanol/ether gave 0.56 g (8%) off-white pure **17**, mp 162–164 °C.

(*Z*)-3-(4-Methylphenyl)-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine Oxalate (14). Zimelidine (**6**, 20 mmol) was lithiated as described for **12** and reacted with 22 mmol of methyl iodide at −60 °C. After addition of water and hexane, the organic layer was evaporated. Extraction with ether, drying ($MgSO_4$), and evaporation of the ether phase gave 4.45 g (88%) of an oil. Recrystallization of the oxalate from ethanol gave 5.1 g (75%) white crystals, mp 183–185 °C.

(*Z*)-3-[4-(Trimethylsilyl)phenyl]-*N*,*N*-dimethyl-3-(3-pyridyl)allylamine Oxalate (15). Lithiation of 20 mmol of **6**, reaction with 26 mmol of trimethylsilyl chloride, and workup as described for **14** gave 6.0 g (75%) of white crystals, mp 185–186 °C.

(*Z*)-*N*,*N*-Dimethyl-3-phenyl-3-(3-pyridyl)allylamine Oxalate (1). Lithiation of 10 mmol of **6**, reaction with water, evaporation of THF, extraction with ether, drying ($MgSO_4$), and evaporation gave a quantitative yield of the base of **1**. This base and 10 mmol of oxalic acid were dissolved in ethanol, and 1 precipitated. After two recrystallizations from ethanol, 1.2 g (37%) of **1**, containing 1.5 equiv of oxalic acid, was obtained, mp 152–155 °C.

Pharmacology. Accumulation of ^{14}C-Labeled 5-HT and ^3H-Labeled NA in Brain Slices. Male albino mice (NMRI) weighing 18–22 g were used in this study. The accumulation of

[^{3}H]noradrenaline and [^{14}C]serotonin in slices of the mouse brain was determined as described previously.[7] 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–Heuseleit's buffer containing 1×10^{-4} M pargyline (this concentration does not inhibit the accumulation of [^{3}H]NA 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 [^{3}H]NA 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 ^{3}H 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 of the inhibitors were determined in quadruplicate. The IC_{50} values were determined from semilogarithmic plots.

The in vivo inhibition of the amine accumulation was determined with 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. ED_{50} values were estimated from semilogarithmic plots.

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Synthesis and Platelet Aggregation Inhibitory Activity of 4,5-Bis(aryl)-2-substituted-thiazoles

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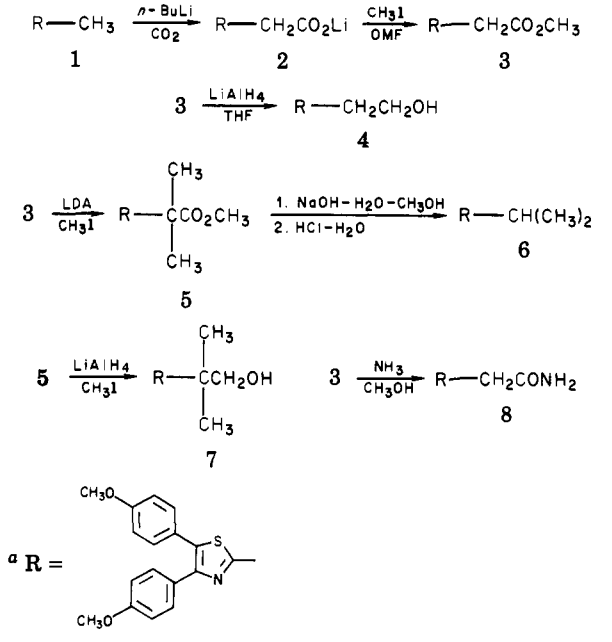
In our continuing effort to discover compounds which inhibit collagen-induced platelet aggregation, we have screened compounds in a mouse pulmonary thromboembolism screen. Methyl 4,5-bis(4-methoxyphenyl)-2-thiazoleacetate (**3**) was very active in the above screen. However, **3** was active for less than 5 min when given orally to guinea pigs. As a result, our synthetic goal was to prepare 2-substituted thiazoles with a much longer duration of activity. This paper describes the preparation of a number 4,5-bis(aryl)-2-substituted-thiazoles and their in vitro and ex vivo activity against collagen-induced platelet aggregation. It was determined that 4,5-bis(4-methoxyphenyl)-2-(trifluoromethyl)thiazole (**16**) is the most promising compound.

Many drugs are known that inhibit platelet function. However, in the past all such drugs were first used for other indications, for example, inflammation and gout (aspirin,[1] dipyridamole,[2] flurbiprofen,[3] and Motrin[4]). While these compounds do inhibit platelet aggregation, their antiplatelet potency is low. Understandably, attempts to demonstrate antithrombotic application of these agents in clinical trials have not met with uniform success.

For successful medical use, potential antithrombotic drugs must inhibit the interactions of platelets with one or more in vivo stimuli which promote platelet thrombi formation. Various mechanisms for thrombi formation have been postulated,[5] one of which is the exposure of collagen or collagen-like substances upon injury to the endothelium. Thus, one reasonable approach to antithrombotic therapy is the use of a potent, selective inhibitor of collagen-induced platelet aggregation.

With the availability of a high-volume mouse pulmonary thromboembolism screen,[6] which detects inhibitors of collagen-induced platelet aggregation, we discovered a novel class of compounds, the thiazoles described in this report. Compound **3** was the first of this series to show activity. However, when tested in the guinea pig using a modified ex vivo assay,[7] compound **3** exhibited a duration of antiplatelet activity of less than 5 min. Upon further investigation, it was shown that under acidic conditions **3** hydrolyzes and readily decarboxylates to give compound **1**. Our synthetic objective, therefore, was to prepare 2-substituted thiazoles which would have greater stability and longer duration of activity in vivo. Structural mod-

Scheme I[a]



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