Jones.[26] In experiments where animals were dosed orally, food was removed 18 h before dosing; intraperitoneal injections were given to unstarved animals.

Blood pressure was measured, under conditions of minimal restraint, with a Bell and Howell pressure transducer linked via a carrier preamplifier to an E and M physiograph. Two pretreatment determinations of blood pressure were made, the animals were dosed with drug or vehicle (isotonic saline), and further measurements were taken after 1, 2, 3, 5, and 22 h.

Pithed Rat Preparations. Experiments were performed on male rats weighing 200–300 g. The animals were pretreated parenterally with either drug or saline (controls) and after a suitable period for absorption were anesthetized with halothane. The trachea was cannulated, the CNS was destroyed by a pithing rod passing through the left orbit and down the spinal cord, and the animals were artificially respired with room air (1 mL/100 g, 50 strokes/min). Pressor responses evoked by stimulation of the entire sympathetic outflow (Gillespie and Muir)[27] or by intravenous injections of noradrenaline or angiotensin were then studied. Following intravenous tubocurarine (1 mg/kg), stimulation was at frequencies of 1, 3, or 6 Hz, 0.5-ms duration, and 20 V was applied for periods of 15 s. The pressor agents noradrenaline (0.1–1 μg/kg) or angiotensin (0.03–0.30 μg/kg) were administered at a constant dose volume (0.1 mL/100 g) via the cannulated femoral vein.

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Registry No. **4a**, 112764-29-1; **4a**·HCl, 112764-30-4; **4b**, 112764-31-5; **4b**·HCl, 112764-32-6; **4c**, 112764-33-7; **4c**, 112764-34-8; **5a**, 112764-35-9; **5b**, 112764-36-0; **5c**, 112764-37-1; **5d**, 112764-38-2; **5e**, 112764-39-3; **6**, 65871-52-5; **7**, 65871-41-2; **8**, 65871-59-2; **9**, 65871-63-8; **10**, 65871-45-6; **11**, 65871-58-1; **12**, 65871-60-5; **13**, 65871-48-9; **14**, 59758-35-9; **14**·HCl, 112764-40-6; **14**·HBr, 112764-41-7; **15**, 65871-51-4; **16**, 112764-42-8; **17**, 112764-43-9; **18**, 65871-65-0; **19**, 65871-73-0; **20**, 65871-50-3; **21**, 65871-46-7; **22**, 65871-47-8; **23**, 65871-72-9; **24**, 104071-22-9; **25**, 65871-61-6; **26**, 104071-21-8; **27**, 65871-68-3; **28**, 65871-49-0; **29**, 65871-71-8; **30**, 112764-44-0; **31**, 65871-66-1; **32**, 65871-69-4; **33**, 65871-64-9; **34**, 65871-67-2; **35**, 112764-45-1; **36**, 112764-46-2; **37**, 65871-56-9; **38**, 112764-47-3; **39**, 65871-62-7; **40**, 112764-48-4; **41**, 65871-70-7; **42**, 112764-49-5; **43**, 65871-57-0; **44**, 112764-50-8; **45**, 112764-51-9; **46**, 112764-52-0; **47**, 112764-53-1; **48**, 112764-54-2; **49**, 112764-55-3; **i** (R = 2-SMe), 112764-56-4; **i** (R = 2-SCH_2CH_2Me), 112764-57-5; **i** (R = 2,6-$(OMe)_2$), 112764-58-6; **ii** (R = 2-SMe), 112764-59-7; **ii** (R = 2-SCH_2CH_2Me), 112764-60-0; **ii** (R = 2,6-$(OMe)_2$), 112764-61-1; **iii** (R = 2-SMe), 3724-10-5; **iii** (R = 2-SCH_2CH_2Me), 21213-10-5; **iii** (R = 2,6-$(OMe)_2$), 1466-76-8; $FeCl_3$, 7705-08-0.

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Antihypertensive Thiadiazoles. 2.[1] Vasodilator Activity of Some 2-Aryl-5-guanidino-1,3,4-thiadiazoles

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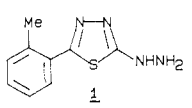
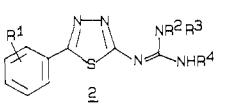
Some 2-aryl-5-guanidino-(or *N*-substituted guanidino)-1,3,4-thiadiazoles and closely related analogues were found to lower blood pressure in metacorticoid (DOCA) hypertensive rats. In the unsubstituted guanidines that exhibited low toxicity, optimum activity resulted when the aryl group was a 2-methylphenyl ring (**11**). Modifications to the guanidine group did not increase antihypertensive activity, but, in the 2-methylphenyl series, the *N*-*n*-butyl- and *N*-(2-methoxyethyl)guanidines (**63** and **78**) and the related iminoimidazolidine **93** were of comparable activity to that of the unsubstituted guanidine **11**. The iminoimidazolidine **93** showed a somewhat longer duration of action than the guanidine derivatives. Preliminary studies in a pithed rat preparation indicated that these thiadiazole derivatives (**11**, **63**, and **93**) lowered blood pressure by a direct relaxant effect on vascular smooth muscle.

The previous paper in this series[1] described the vasodilator activity of some hydrazinothiadiazoles, exemplified by the potent compound **1**. With the objective of retaining vasodilator activity but reducing the likelihood of toxic effects, the hydrazine group in **1** was replaced with a guanidine moiety (**2**). Compounds containing guanidine



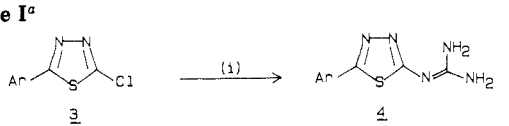
1



2

groups have frequently been found to produce antihypertensive effects, in other series, through a number of modes of action, including adrenergic neurone blockade,[2] vasodilation,[3] α_2-adrenoreceptor agonism,[4] and unclassified mechanisms.[5] Some of the unsubstituted guanidinothiadiazoles **4** (Scheme I), though generally less potent than the hydrazines (**1**), retained a similar vasodilator profile, but the length of action was deemed too short.

Scheme I[a]



3 **4**

[a] (i) $[NH_2C(=NH)NH_2]_2 \cdot H_2CO_3/K_2CO_3$/dioxane.

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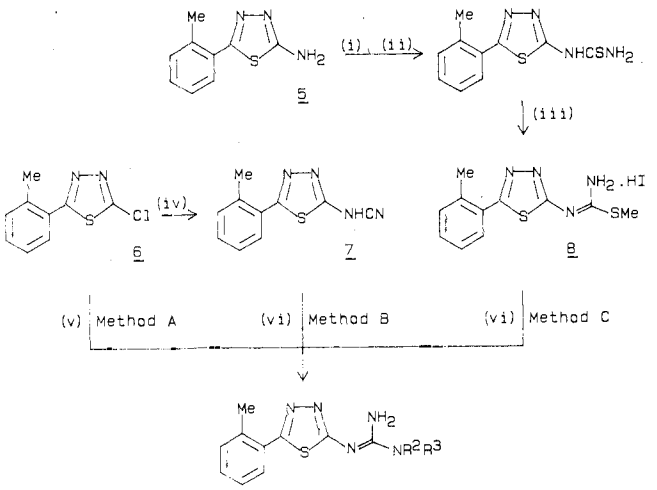
Scheme II[a]



[a] (i) MeO_2CNCS; (ii) NaOH; (iii) MeI; (iv) NaH/NH_2CN; (v) $NH_2C(=NH)NR^2NR^3$; (vi) R^2R^3NH/n-BuOH.

Reasoning that the duration of the antihypertensive effect might be influenced by increasing the lipophilicity of these compounds, the effects of alkyl substitution in the guanidine group were also examined, and structure–activity studies in these series are now reported.

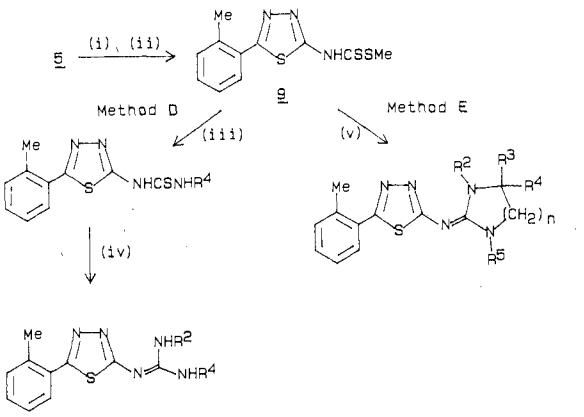
Chemistry

The unsubstituted guanidines **4** (Tables I and II) were prepared in moderate yields from previously described[1] chlorothiadiazole intermediates **3** by treatment with excess guanidine in dioxane (Scheme I).

A 2-methylphenyl substituent, which conferred highest activity in the guanidines **4** (see later) and was synthetically readily accessible, was retained in the majority of the N-alkylated derivatives prepared.

The N-substituted thiadiazole guanidines (Table III) and the cyclic analogues (Table IV) were synthesized by general methods[6,7] A–E from 2-chloro- or 2-amino-thiadiazoles **6** and **5**, respectively (Schemes II and III). 1-Alkylated and 1,1-dialkylated compounds were obtained directly by treatment of **6** with a substituted guanidine (method A) or by reaction of a primary or secondary amine with the cyanamide intermediate **7** (method B). Reaction of amines with the (methylthio)uronium iodide **8** (method C) also gave the required guanidines, but, less conveniently and in lower overall yields. Sequential treatment of the *S*-methyl dithiocarbamate[8] **9** (Scheme III) with an amine, followed by a second amine with the presence of mercury(II) oxide,[9] gave 1,3-disubstituted thiadiazole guanidines (method D) while cyclic analogues were obtained by reaction of **9** with a diamine (method E).

Scheme III[a]



[a] (i) $CS_2/KOH/DMF$; (ii) MeI; (iii) R^4NH_2/n-BuOH; (iv) $R^2NH_2/Hg(II)O$; (v) $R^2NHC(R^3R^4)(CH_2)_nNHR^5/n$-BuOH.

Compounds (**80–83**, **94**, and **95**) with aryl groups other than 2-methylphenyl were prepared by similar methods to those described above from the appropriate intermediates. The (methylamino)imidazoline **98** was obtained by reaction of the *N*-methyl analogue of the *S*-methyl dithiocarbamate **9** with ethylenediamine. Reaction of aminoacetaldehyde dimethyl acetal with the cyanamide **7** followed by acid treatment furnished the imidazole **100**.

The thiadiazole guanidines and the cyclic analogues (Tables I and II) were weak bases (pK_a = 4.50–5.29) and are thought to exist predominantly, in solution, in the tautomer shown. The higher basicity of the (methylamino)imidazoline **98** (pK_a = 8.27), in which the double bond cannot be in conjugation with the thiadiazole ring, supports this view.

Results and Discussion

The antihypertensive activity of the guanidines was determined in metacorticoid (DOCA) hypertensive rats. Results are expressed as percentage reductions in mean arterial blood pressure (MABP) compared with pretreatment controls. For clarity of presentation, the primary screening data on the guanidines (Tables I and II) and the N-substituted and cyclic analogues (Tables III and IV) are discussed separately.

Guanidines (Tables I and II). At the standard oral dose of 100 mg/kg, the 5-phenyl derivative **10** produced a moderate (30%) reduction in blood pressure. An examination of the effect on antihypertensive activity of substitution in the phenyl ring of **10**, with groups encompassing a range of sizes, lipophilicity, and electronic characteristics, highlighted three ortho-substituted compounds (**11**, **28**, and **29**) with enhanced activity compared with **10**. Some other 2-substituted analogues (e.g. **14**, **17**, **20**, and **23**) retained a similar level of activity to **10**, but, with the exception of the dimethylated compound **43**, the introduction of groups into the 3- or 4-position of the phenyl ring either reduced or abolished antihypertensive activity in this series. Of the compounds synthesized in which the phenyl group in **10** was replaced by other ring systems (Table II), only the close analogue **56** with a bioisosteric 2-thienyl group retained significant activity.

The increases in potency seen with some of these 2-substituted phenyl compounds (**11**, **28**, and **29**) parallel those observed in the related 2-aryl-5-hydrazino-1,3,4-thiadiazole series.[1] However, the marginal antihypertensive effects noted for the 2-(methylsulfinyl)phenyl and 2-ethylphenyl compounds (**31** and **33**) contrasted markedly with high activity associated with these particular substituents in the hydrazine series. Also in contrast to their

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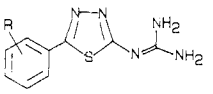
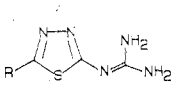
Table I



no.	R	mp, °C	recrystn solvent	formula[a]	yield, %	reduction[b] in MABP,[c,d] % ± SEM
10	H	263–265	DMF	$C_9H_8N_5S\cdot HCl$	30	30 ± 4
11	2-Me	239–242	MeOH–Et_2O	$C_{10}H_{11}N_5S\cdot HCl$	22	41 ± 4
						36 ± 2 (50 mg/kg, po)
12	3-Me	277–279	EtOH–MeOH	$C_{10}H_{11}N_5S\cdot HCl$	29	19 ± 3
13	4-Me	>300	EtOH–Et_2O	$C_{10}H_{11}N_5S\cdot HCl$	43	IA[e]
14	2-F	268–269	EtOH	$C_9H_8FN_5S\cdot HCl$	32	31 ± 5
15	3-F[f]	267–269	dioxane	$C_9H_8FN_5S\cdot HCl$	38	20 ± 1
16	4-F[g]	268–270	DMF	$C_9H_8FN_5S\cdot HCl$	13	20 ± 2
17	2-Cl	226–229	MeOH	$C_9H_8ClN_5S\cdot HCl$	20	30 ± 3
18	3-Cl	253–257	MeOH–Et_2O	$C_9H_8ClN_5S\cdot HCl$	44	12 ± 2
19	4-Cl	>300	DMF	$C_9H_8ClN_5S\cdot HCl$	28	18 ± 6 (100 mg/kg, ip)
20	2-CF_3	215–218	MeOH–Et_2O	$C_{10}H_8F_3N_5S\cdot HCl$	24	26 ± 7
21	3-CF_3	258–260	MeOH	$C_{10}H_8F_3N_5S\cdot HCl$	51	14 ± 4
22	4-CF_3	>300	MeOH	$C_{10}H_8F_3N_5S\cdot HCl$	41	18 ± 2
23	2-OMe	235–237	MeOH–Et_2O	$C_{10}H_{11}N_5OS\cdot HCl$	13	26 ± 6
24	3-OMe	257–259	MeOH	$C_{10}H_{11}N_5OS\cdot HCl$	20	IA[e]
25	4-OMe[f]	261–262	DMF	$C_{10}H_{11}N_5OS\cdot HCl$	49	28 ± 2 (100 mg/kg, ip)
26	2-NO_2	244–250	MeOH	$C_9H_8N_6O_2S\cdot HCl$	29	17 ± 2
27	4-NO_2[f]	>280	EtOH	$C_9H_8N_6O_2S\cdot HCl$	33	IA[e]
28	2-Br	220–224	MeOH–Et_2O	$C_9H_8BrN_5S\cdot HCl$	23	41 ± 4
						29 ± 2 (50 mg/kg, po)
29	2-I	203–206	EtOH–Et_2O	$C_9H_8IN_5S\cdot HCl$	40	41 ± 6
						28 ± 5 (50 mg/kg, po)
30	2-SMe	202–207	MeOH–Et_2O	$C_{10}H_{11}N_5S_2\cdot HCl$[h]	31	13 ± 4
31	2-SOMe	239–241	MeOH–Et_2O	$C_{10}H_{11}N_5OS_2\cdot HCl$	24	15 ± 4
32	2-SO-*n*-Pr	160–163	MeOH–Et_2O	$C_{12}H_{15}N_5OS_2\cdot HCl$	42	13 ± 3
33	2-Et	243–244	EtOAc	$C_{11}H_{13}N_5S$[i]	10	12 ± 4
34	2-*t*-Bu	192–194	EtOAc	$C_{13}H_{17}N_5S$	14	22 ± 4
35	2-OH[j]	>300	MeOH	$C_9H_9N_5OS\cdot HBr$	47	IA[e]
36	2-O-*n*-Pr	146–148	*i*-PrOH–petroleum ether	$C_{12}H_{15}N_5OS\cdot HCl$[k]	19	12 ± 3
37	2-Ph	235–238	MeOH	$C_{15}H_{13}N_5S\cdot HCl$	34	IA[e]
38	2-NH_2[l]	264–265	MeOH–Et_2O	$C_9H_{10}N_6S\cdot 2HCl$	28	14 ± 1
39	2,3-Me_2	248–250	MeOH	$C_{11}H_{13}N_5S\cdot HCl$	42	14 ± 4
40	2,4-Me_2	228–229	EtOH	$C_{11}H_{13}N_5S\cdot HCl$	41	IA[e]
41	2,5-Me_2	242–244	MeOH–Et_2O	$C_{11}H_{13}N_5S\cdot HCl$	25	IA[e]
42	2,6-Me_2	229–231	EtOH–Et_2O	$C_{11}H_{13}N_5S\cdot HCl$	10	IA[e]
43	3,4-Me_2	271–274	MeOH	$C_{11}H_{13}N_5S\cdot HCl$	22	33 ± 4
44	3,5-Me_2	253–255	EtOH	$C_{11}H_{13}N_5S\cdot HCl$	24	18 ± 3
45	2,6-Cl_2	252–253	EtOAc	$C_9H_7Cl_2N_5S$	18	34 ± 3 (100 mg/kg, ip)
46	3,4-Cl_2	269–270	MeOH	$C_9H_7Cl_2N_5S\cdot HCl$	62	15 ± 6
47	2,6-$(OMe)_2$	250–251	EtOAc	$C_{11}H_{13}N_5O_2S$	17	16 ± 2
48	3,4-$(OMe)_2$	228–230	*i*-PrOH–MeOH	$C_{11}H_{13}N_5O_2S\cdot HCl$	23	21 ± 6
49	2-Me-4,5-$(OMe)_2$[g]	232–235	EtOH	$C_{12}H_{15}N_5O_2S\cdot HCl$	25	24 ± 2
50	2-Me-4-F	226–230	MeOH	$C_{10}H_{10}FN_5S\cdot HCl$	52	34 ± 4
51	2-Me-5-F	188–90	EtOH	$C_{10}H_{10}FN_5S\cdot HCl$	41	21 ± 4
hydralazine						39 ± 2 (5 mg/kg, po)
minoxidil						42 ± 3 (10 mg/kg, po)

[a] Elemental analyses for C, H, N were within ±0.4% of the calculated values except where otherwise indicated. [b] Maximum percentage reduction, compared to the mean of two pretreatment control values, in MABP in DOCA hypertensive rats (n = 3–5). [c] Mean arterial blood pressure = diastolic blood pressure + one-third pulse pressure. [d] Results refer to an oral dose of 100 mg/kg except where otherwise indicated. [e] Inactive; maximum percentage fall in MABP <10%. [f] The intermediate 2-aminothiadiazole was obtained from the appropriate arylthiosemicarbazone, ref 1. [g] As *f* from the appropriate aroylthiosemicarbazide, ref 1. [h] N: calcd 23.21, found 23.88. [i] N: calcd 28.32, found 27.72. [j] From **23** with BBr_3 (for the method, see example **30**, ref 1). [k] N: calcd, 22.32; found, 21.85. [l] See the Experimental Section.

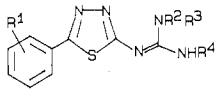
Table II



no.	R	mp, °C	recrystn solvent	formula	yield, %	reduction[b] in MABP,[c,d] % ± SEM
52	cyclohexyl[e]	267–269	EtOH	$C_9H_{14}N_5S$	25	IA[f]
53	1-naphthyl	253–256	EtOH	$C_{13}H_{11}N_5S\cdot HCl$	19	20 ± 4
54	2-pyridyl	267–269	MeOH	$C_8H_8N_6S\cdot HCl$	21	19 ± 1
55	2-furyl	221–223	MeOH	$C_7H_7N_5OS\cdot HCl$	32	24 ± 4
56	2-thienyl	269–272	MeOH	$C_7H_7N_5S_2\cdot HCl$	40	32 ± 4
57	3-methyl-2-thienyl	>280	MeOH	$C_8H_9N_5S_2\cdot HCl$	36	14 ± 5

[a–d] See corresponding footnotes in Table I. [e] See footnote *f* in Table I. [f] See footnote *e* in Table I.

Table III



no.	R^1	R^2	R^3	R^4	method	mp, °C	recrystn solvent	formula[a]	yield, %	reduction[b] in MABP,[c,d] % ± SEM
58	2-Me	Me	H	H	A	155–156	EtOAc	$C_{11}H_{13}N_5S$	9	31 ± 4
59	2-Me	Me	Me	H	A	220–223	MeOH	$C_{12}H_{15}N_5S$·HCl	3	18 ± 4
60	2-Me	Me	H	Me	A	186–190	MeOH	$C_{12}H_{15}N_5S$·HCl	3	27 ± 7
61	2-Me	*n*-Pr	H	H	C	179–181	$CHCl_3$–petroleum ether	$C_{13}H_{17}N_5S$·HCl	38	32 ± 5
62	2-Me	*i*-Pr	H	H	C	202–205	$CHCl_3$–petroleum ether	$C_{13}H_{17}N_5S$·HCl	48	23 ± 4
63	2-Me	*n*-Bu	H	H	C	178–180	EtOH–Et_2O	$C_{14}H_{19}N_5S$·HCl	38	39 ± 4
64	2-Me	*t*-Bu	H	H	C	208–212	EtOH	$C_{14}H_{19}N_5S$·HCl	14	18 ± 1
65	2-Me	*n*-Bu	H	Me	D	176–178	EtOH–Et_2O	$C_{15}H_{21}N_5S$·HCl	47	28 ± 3
66	2-Me	*n*-pentyl	H	H	C	140–145	EtOH–Et_2O	$C_{15}H_{21}N_5S$·HCl	35	23 ± 2
67	2-Me	$CH_2CH{=}CH_2$	H	H	C	186–188	EtOH–Et_2O	$C_{13}H_{15}N_5S$·HCl	38	28 ± 2
68	2-Me	Ph	H	H	B	195–197	EtOH	$C_{16}H_{15}N_5S$·HCl	30	IA[e]
69	2-Me	CH_2Ph	H	H	C	205–210	EtOH–Et_2O	$C_{17}H_{17}N_5S$·HCl	36	12 ± 3
70	2-Me	$(CH_2)_2Ph$	H	H	C	165–168	$CHCl_3$–petroleum ether	$C_{18}H_{19}N_5S$·HCl	38	29 ± 1
71	2-Me	c-C_4H_7	H	H	B	199–200	EtOH–Et_2O	$C_{14}H_{17}N_5S$·HCl	22	IA[e]
72	2-Me	c-C_5H_9	H	H	C	207–211	EtOH–Et_2O	$C_{15}H_{19}N_5S$·HCl	31	20 ± 3
73	2-Me	$CH_2CH_2CH_2CH_2$		H	C	230–231	EtOH–Et_2O	$C_{14}H_{17}N_5S$·HCl	40	IA[e]
74	2-Me	$CH_2CH_2OCH_2CH_2$		H	C	186–189	EtOH–Et_2O	$C_{14}H_{17}N_5OS$·HCl	63	16 ± 3
75	2-Me	$CH_2CH_2N(Me)CH_2CH_2$		H	C	228–230	EtOH	$C_{15}H_{20}N_6S$·2HCl	32	18 ± 5
76	2-Me	CH_2CH_2OH	H	H	C	168–172	MeOH–Et_2O	$C_{12}H_{15}N_5OS$·HCl	19	35 ± 3
77	2-Me	$CH_2CH_2CH_2OH$	H	H	C	169–172	EtOH–Et_2O	$C_{13}H_{17}N_5OS$·HCl	25	24 ± 3
78	2-Me	CH_2CH_2OMe	H	H	B	165–166	MeOH–Et_2O	$C_{13}H_{17}N_5OS$·HCl	82	37 ± 2
79	2-Me	$CH_2CH_2CH_2OMe$	H	H	B	114–116	dioxane–Et_2O	$C_{14}H_{19}N_5OS$·HCl	17	33 ± 5
80	2-I	CH_2CH_2OMe	H	H	B	168–169	EtOH–Et_2O	$C_{12}H_{14}IN_5OS$·HCl	51	33 ± 3
81	2,4-Me_2	CH_2CH_2OMe	H	H	B	179–181	EtOH	$C_{14}H_{19}N_5OS$·HCl	47	31 ± 2
82	2-Me-4-F	CH_2CH_2OMe	H	H	B	187–190	EtOH–Et_2O	$C_{13}H_{16}FN_5OS$·HCl	49	33 ± 5
83	3,4-$(OMe)_2$	CH_2CH_2OMe	H	H	B	199–201	EtOH–Et_2O	$C_{14}H_{19}N_5O_3S$·HCl	20	20 ± 7
84	2-Me	CH_2CH_2OEt	H	H	B	126–129	EtOH–Et_2O	$C_{14}H_{19}N_5OS$·HCl[f]	42	34 ± 5
85	2-Me	$CH_2CH(OH)Me$	Me	H	B	164–168	EtOH–Et_2O	$C_{14}H_{19}N_5OS$·HCl	15	21 ± 2
86	2-Me	$CH_2CH_2CH_2CH_2CH_2O$	H	H	B	161–163	EtOH–Et_2O	$C_{15}H_{19}N_5OS$·HCl[g]	33	17 ± 3
87	2-Me	CH_2CH_2SMe	H	H	B	171–173	EtOH–Et_2O	$C_{13}H_{17}N_5S_2$·HCl	25	18 ± 3
88	2-Me	CH_2CH_2NHAc	H	H	B	168–170	EtOH	$C_{14}H_{18}N_6OS$	25	21 ± 5
89	2-Me	$CH_2CH_2NH_2$	H	H	*i*	208–210	MeOH	$C_{12}H_{16}N_6S$·2HCl[h]	34	32 ± 2
90	2-Me	$CH_2CH_2CH_2NMe_2$	H	H	C	239–243	EtOH–Et_2O	$C_{15}H_{22}N_6S$·2HCl	25	20 ± 3
91	2-Me	$CH_2CH_2CH_2NMe_2$	H	*n*-Bu	D	177–180	EtOH–Et_2O	$C_{19}H_{30}N_6S$·2HCl	63	IA[e]
92	2-Me	OMe	H	H	B	165–167	EtOH–Et_2O	$C_{11}H_{13}N_5OS$·HCl	14	29 ± 3
hydralazine										39 ± 2 (5 mg/kg, po)

[a–e] See corresponding footnotes in Table I. [f] H: calcd, 5.90; found, 6.36. [g] C: calcd, 50.91; found, 50.54. [h] N: calcd 24.06, found 24.69. [i] See the Experimental Section.

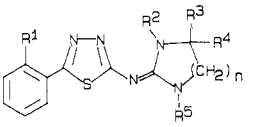
hydrazino counterparts, the guanidines **11** and **28** showed no overtly toxic effects in DOCA rats up to an oral dose of 200 mg/kg. At this dose, blood pressure was reduced by a similar extent (approximately 40%) as at the lower dose levels with only a slight increase in heart rate. In line with these observations, the acute, oral toxicity of **11** and **28** in male rats was very low (LD_{50} > 1000 mg).

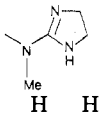
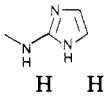
N-Substituted Guanidines and Cyclic Analogues (Tables III and IV). The 1-(alkylguanidino)thiadiazoles **58**, **61**, and **63** all produced significant hypotensive effects, the *n*-butyl compound **63** being comparable to the unsubstituted guanidine **11**. Analogous compounds with branched alkyl chains (**62** and **64**) or cycloalkyl groups (**71** and **72**) and the longer straight chain derivative **66** were all less active. Guanidines substituted with hydroxy- or alkoxyalkyl groups were of more interest. The 2-hydroxyethyl compound **76** produced a marked reduction in MABP though the homologue **77** was less active. The corresponding methyl and ethyl ethers (**78** and **84**) of **76** and the methyl ether (**79**) of **77** all produced substantial antihypertensive effects. Other guanidines containing the 2-methoxyethyl substituent (**80–82**) were of comparable activity. Related compounds in which the oxygen atom of the side chain was incorporated in a five-membered ring (**86**) or replaced by sulfur (**87**) had little activity. The analogous 2-aminoethyl derivative **89** was unusual in that a significant tachycardia (28% increase from control values) was observed. The remainder of the guanidines, with the exception of the 1-methyl compound **58** (25% increase), had little effect on the heart rate of DOCA hypertensive rats.

Disubstitution in these thiadiazole guanidines generally reduced antihypertensive activity. The 1,1-disubstituted compounds **59**, **73–75**, and **85** were all either inactive or weakly active. Of the 1,3-disubstituted compounds examined, the dimethyl derivative **60** retained the activity of the monomethylated analogue **58**, but the marked antihypertensive activity of the 1-*n*-butyl compound **63** was reduced by 3-methyl substitution (**65**) and abolished on introduction of a 3-(dimethylamino)propyl group (**91**).

Among the cyclic guanidines examined, potent hypotensive activity was associated exclusively with the iminoimidazolidine **93**. Replacing the 2-methylphenyl ring in **93** with other groups (**94** and **95**), substitution in the guanidine group (**96–98**) or changing the imidazolidine ring to tetrahydropyrimidine (**101**) all drastically reduced ac-

Table IV



no.	R^1	R^2	R^3	R^4	R^5	n	method	mp, °C	recrystn solvent	formula	yield, %	reduction[b] in MABP,[c,d] % ± SEM
93	2-Me	H	H	H	H	1	E	231–232	$CHCl_3$–petroleum ether	$C_{12}H_{13}N_5S$·HCl	60	43 ± 3
94	2-I	H	H	H	H	1	E	223–227	EtOH–Et_2O	$C_{11}H_{10}IN_5S$·HCl	17	33 ± 5
95	2,4-Me_2	H	H	H	H	1	E	238–240	EtOH–Et_2O	$C_{13}H_{15}N_5S$·HCl	30	24 ± 4
96	2-Me	Me	H	H	H	1	E	208–210	EtOH	$C_{13}H_{15}N_5S$·HCl	20	IA
97	2-Me	H	Me	Me	H	1	E	194–196	EtOH–Et_2O	$C_{14}H_{17}N_5S$·HCl	7	15 ± 3
98	2-Me						E	222–224	EtOH–Et_2O	$C_{13}H_{15}N_5S$·HCl·0.5H_2O	5	IA
99	2-Me	Me	H	H	Me	1	E	172–178	*i*-PrOH–Et_2O	$C_{14}H_{17}N_5S$·HCl	13	IA
100	2-Me						E	205–209	EtOH–Et_2O	$C_{12}H_{11}N_5S$·HCl·0.5H_2O	10	40 ± 4
101	2-Me	H	H	H	H	2	E	208–211	EtOH–Et_2O	$C_{13}H_{15}N_5S$·HCl	39	13 ± 2

[a-d] See corresponding footnotes in Table I. [e] See the Experimental Section.

Table V. Duration of Action: DOCA Hypertensive Rats

	reduction in MABP,[a] % ± SEM (h)[b]		summation MABP[c]	
no.	100 mg/kg, po	50 mg/kg, po	100 mg/kg, po	50 mg/kg, po
11	41 ± 4 (3)	36 ± 2 (2)	167	115
63	39 ± 4 (5)	31 ± 4 (5)	159	126
78	37 ± 2 (3)	29 ± 4 (3)	157	113
93	43 ± 3 (3)	28 ± 4 (3)	194	117
1		48 ± 2 (5)		206

[a] See footnotes *b* and *c*, Table I. [b] Time (hours) after dosing at which peak hypotensive response occurred. [c] Summation of the percentage reductions, compared to pretreatment controls, in MABP of DOCA hypertensive rats (n = 5) at 1, 2, 3, 5, and 8 h after the stated oral dose.

tivity. The related imidazole **100** showed good activity, but solutility problems discouraged further work on this compound.

The data in Table V show a summation of the percentage reductions in blood pressure in DOCA rats taken at standard intervals over an 8-h period and gives an indication of the length of action of some of the more active guanidines. The duration of the hypotensive response produced by the guanidine **11** was not increased in the N-substituted analogues (**63** and **78**) although with the *n*-butyl compound **63** the maximum reduction in MABP occurred later than with the other two derivatives. The imidazolidine **93** at the higher dose level maintained substantial reductions in blood pressure over a somewhat longer time scale than the guanidines but was clearly a much less effective antihypertensive agent than the related hydrazine **1**. The pronounced difference in the duration of action of the guanidino- and the hydrazinothiadiazoles may be due to te finding[1] that the latter or a metabolite can bind irreversibly to elastic elements in blood vessel walls.

The mechanism of the hypotensive action of these compounds was examined in a pithed rat preparation. The effects of the guanidines **11**, **28**, **63**, and **78** and the imidazolidine **93**, in this model, on the increases in blood pressure evoked by sympathetic stimulation or administration of noradrenaline or angiotensin are shown in Table VI. The imidazolidine **93** and the guanidines **11**, **28**, and **63** showed a similar profile to the direct acting vasodilator hydralazine, producing an inhibition of the hypertensive responses to each of the pressor stimuli. In contrast, the 2-methoxyethyl derivative **78**, though antagonizing the pressor responses to noradrenaline and angiotensin, was without effect on those due to electrical stimulation. On the basis of these initial studies, it would appear that while

Table VI. Effects of Thiadiazole Guanidine Derivatives on Pressor Responses Induced by Sympathetic Stimulation, Noradrenaline, and Angiotensin in the Pithed Rat[a]

	increase in diastolic blood pressure, mmHg								
	electrical stimulation, Hz			noradrenaline, μg/kg, iv			angiotensin, μg/kg, iv		
treatment	1	3	6	0.1	0.3	1.0	0.03	0.1	0.3
control[b]	28 ± 3	54 ± 4	62 ± 4	19 ± 3	40 ± 4	69 ± 3	6 ± 1	19 ± 2	41 ± 4
11[c]	13 ± 2	29 ± 4	35 ± 5	12 ± 1	23 ± 1	39 ± 2	2 ± 1	9 ± 1	22 ± 1
control[b]	38 ± 3	58 ± 3	66 ± 3	19 ± 1	38 ± 1	62 ± 3	5 ± 1	14 ± 1	30 ± 2
28[c]	17 ± 2	31 ± 4	38 ± 5	13 ± 1	27 ± 2	50 ± 3	3 ± 1	7 ± 1	17 ± 2
control[b]		43 ± 4			59 ± 4			50 ± 6	
63[d]		20 ± 4			42 ± 2			23 ± 3	
control[e]	30 ± 2	55 ± 2	69 ± 2	22 ± 3	37 ± 3	64 ± 1	20 ± 2	35 ± 3	58 ± 3
78[c]	30 ± 2	52 ± 3	65 ± 4	13 ± 2	25 ± 3	45 ± 4	14 ± 1	28 ± 3	44 ± 2
93[c]	17 ± 3	34 ± 4	45 ± 5	10 ± 1	21 ± 2	44 ± 3	15 ± 2	27 ± 2	43 ± 2
control[b]	52 ± 4	77 ± 3	93 ± 3	48 ± 8	54 ± 5	75 ± 5	33 ± 3	52 ± 4	77 ± 4
hydralazine[f]	28 ± 3	42 ± 3	54 ± 4	8 ± 2	15 ± 1	28 ± 2	8 ± 1	21 ± 2	38 ± 2

[a] For the general method, see ref 1. [b] Isotonic saline, ip. [c] A dose of 50 mg/kg, ip, was administered to groups of five rats 2 h prior to the pithing procedure. [d] As in footnote *c*, 25 mg/kg, ip, at 2 h. [e] Control group for both **78** and **93**. [f] As in footnote *c*, 5 mg/kg, ip, at 1 h.

11, 28, 63, and 93 produce a direct relaxant effect on vascular smooth muscle, the guanidine 78 may exert its antihypertensive effects by a different mechanism.

Conclusion

In fulfillment of our objectives, guanidino-1,3,4-thiadiazoles were identified that lowered blood pressure by a direct relaxant effect on vascular smooth muscle and were markedly less toxic than the related hydrazine 1. Structure–activity studies showed that optimum activity resulted when the thiadiazole ring was substituted with a 2-methylphenyl group and when the thiadiazole guanidine moiety was either unsubstituted (11), monosubstituted with a group comprising a four-atom chain (e.g. 63), or in the form of an iminoimidazolidine function (93). The relatively low potency and short duration of action of these guanidine derivatives mitigated against their further development.

Experimental Section

Chemistry. Melting points, which are uncorrected, were determined in a Büchi apparatus with glass capillary tubes or a Kofler micro hot stage apparatus. IR and NMR spectra were recorded on Perkin-Elmer 700 and Varian Associates T-60 instruments, respectively. Where analyses are indicated only by symbols of elements, results obtained were within ±0.4% of the theoretical values. Where purification was carried out by column chromatography, silica gel refers to Kieselgel 60, 70–230 mesh ASTM.

Method A. The guanidines 2 were prepared from the appropriate 2-aryl-5-chloro-1,3,4-thiadiazoles (3).[1] The procedure is illustrated with a representative example.

2-Guanidino-5-(2-methylphenyl)-1,3,4-thiadiazole Hydrochloride (11). Guanidine carbonate (9.54 g, 0.0529 mol) was stirred at room temperature for 2 h with a solution of NaOH (4.23 g, 0.1057 mol) in MeOH (120 mL). After filtration and removal of MeOH in vacuo, 2-chloro-5-(2-methylphenyl)-1,3,4-thiadiazole (5.60 g, 0.0266 mol) in dry dioxane (150 mL) was added, and the mixture was heated at reflux for 8 h. The solvent was removed, water was added, and the mixture was filtered. The resultant solid was warmed for 15 min with 2 N HCl (25 mL), cooled, and filtered, and the product was recrystallized from MeOH–Et_2O to give 11 (1.60 g, 30%): mp 239–242 °C; ^1H NMR (DMSO-d_6) δ 2.50 (s, 3 H, Me), 3.36 (br s, 2 H, NH_2), 7.02–7.75 (m, 6 H, Ar H and NH). Anal. ($C_{10}H_{11}H_5S$·HCl) C, H, N.

2-(2-Aminophenyl)-5-guanidino-1,3,4-thiadiazole Dihydrochloride (38). A mixture of 26 (0.83 g, 0.002 76 mol) with iron powder (0.52 g, 0.009 31 mol) in 50% aqueous EtOH (62 mL) was heated at reflux for 1 h. The guanidine hydrochloride 26 initially dissolved, and the product then precipitated from the hot solution and was removed by filtration. This solid was extracted with portions of hot MeOH (3 × 40 mL), the combined extracts were evaporated, and the residue was stirred with NH_3 (0.88 g/mL). The crude base was collected by filtration, washed with water, dried, and converted to a hydrochloride salt. Crystallization from MeOH–Et_2O gave the amino compound 38 (0.24 g, 28%), mp 264–265 °C. Anal. ($C_9H_{10}N_6S$·2HCl) C, H, N.

Methods B–E. The preparative procedures (B–E) are exemplified by a representative example in each case.

Method B. 1-(2-Methoxyethyl)-2-[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]guanidine Hydrochloride (78). A stirred solution of cyanamide (6.0 g, 0.142 7 mol) in anhydrous DMF (220 mL) under a nitrogen atmosphere was treated with sodium hydride (50% oil dispersion, 6.7 g, 0.1396 mol) in portions over 15 min. After the mixture was stirred for a further 15 min at room temperature, a solution of the 2-chlorothiadiazole 6 (12.0 g, 0.0570 mol) in anhydrous DMF (30 mL) was added, and the mixture heated at 100 °C for 1.5 h. The solvent was removed under reduced pressure, and water was added to the residue. Acidification with 2 N HCl, to pH 3, and filtration gave the substantially pure cyanamide 7 (14.0 g). A sample recrystallized from EtOAc failed to show a characteristic melting point. Anal. ($C_{10}H_8N_4S$) C, H, N. (The cyanamide precursors to compounds 81–83 were prepared in a similar manner and used without purification.) A solution of the cyanamide 7 (2.16 g, 0.010 mol) and 2-methoxyethylamine (0.90 g, 0.0120 mol) in *n*-BuOH (20 mL) was heated at reflux for 1.5 h. The solvent was evaporated, and residue was converted to a hydrochloride salt and recrystallized (MeOH–Et_2O) to give 78 (2.79 g) (82%): mp 165–166 °C; ^1H NMR (DMSO-d_6) δ 2.50 (s, 3 H, Me), 3.33 (s, 3 H, OMe), 3.5–3.8 (br s, 4 H, CH_2CH_2), 7.2–7.8 (m, 4 H, Ar H), 8.5–9.1 (m, 3 H, NH). Anal. ($C_{13}H_{17}N_5OS$·HCl) C, H, N.

Method C. 1-*n*-Butyl-2-[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]guanidine Hydrochloride (63). A mixture of 2-amino-5-(2-methylphenyl)-1,3,4-thiadiazole (5) (20.0 g, 0.1046 mol) and carbomethoxyisothiocyanate (14.5 g, 0.1238 mol)[13] in dry toluene (400 mL) was heated at reflux for 1.5 h. The solvent was evaporated, aqueous 2N NaOH (400 mL) was added, and the mixture was heated on a steam bath for 2 h. The solution was cooled and filtered, and the filtrate was acidified with 2 N HCl. The product was isolated by filtration, dried, and crystallized from 2-propanol to give *N*-[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]-thiourea (9.7 g) (63%), mp 221–224 °C. Anal. ($C_{10}H_{10}N_4S_2$) C, H, N. The thiourea (1.0 g, 0.0040 mol) and iodomethane (0.57 g, 0.0040 mol) in ethanol (50 mL) were heated at reflux for 3 h. The solution was concentrated to approximately $^1/_3$ volume, Et_2O was added, and the mixture was kept in a refrigerator for 18 h. Filtration and recrystallization from EtOH–Et_2O gave 2-methyl-1-[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]isothiourea hydroiodide (8) (0.31 g) (20%), mp 242–244 °C. Anal. ($C_{11}H_{12}N_4S_2$·HI) C, H, N. A solution of the thiouronium salt (3.0 g, 0.0076 mol) and *n*-butylamine (0.56 g, 0.0077 mol) in *n*-BuOH (30 mL) was heated at reflux for 16 h. The solvent was evaporated, aqueous $NaHCO_3$ was added, and the product was extracted into $CHCl_3$. The extracts were dried and evaporated, and the resultant solid was heated with 2 N HCl (15 mL) on a steam bath for 5 min. After cooling, the hydrochloride salt obtained by filtration was recrystallized from EtOH–Et_2O to give 63 (0.95 g) (38%): mp 177–180 °C; ^1H NMR (DMSO-d_6) δ 0.85–1.7 (m, 7 H, CH_2CH_2Me), 2.50 (s, 3 H, Me), 3.15–3.65 (m, 2 H, NCH_2), 7.25–7.70 (m, 4 H, Ar H), 8.5–9.1 (m, 3 H, NH). Anal. ($C_{14}H_{19}N_5S$·HCl) C, H, N.

Method D. 1-*n*-Butyl-3-[3-(dimethylamino)propyl]-2-[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]guanidine Hydrochloride (91). In a similar method to that described by Shams El-Dine and Clauder,[8] a mixture of 2-amino-5-(2-methylphenyl)-1,3,4-thiadiazole (5) (19.13 g, 0.1000 mol), KOH pellets (5.70 g, 0.1016 mol), and carbon disulfide (7.0 g, 0.102 6 mol) in DMF (50 mL) was vigorously stirred at room temperature in a stoppered flask for 18 h. Ether was added, and crude potassium [5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]dithiocarbamic acid (27.6 g) was isolated as a yellow solid by filtration. The dithiocarbamic acid salt (27.6 g, 0.0950 mol) was dissolved in MeOH (275 mL) at reflux, and iodomethane (14.0 g, 0.0986 mol) was added dropwise over 15 min. After being heated at reflux for a further 0.5 h, the mixture was concentrated to a small volume, water was added, and the resultant yellow solid was isolated by filtration. The solid was washed with boiling MeOH (2 × 50 mL) and dried to give *S*-methyl [5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]dithiocarbamate (9) (16.5 g) (59%), mp 190–193 °C. Anal. ($C_{11}H_{11}N_3S_3$) C, H, N. The dithiocarbamate (5.00 g, 0.0178 mol) and *n*-butylamine (2.4 g, 0.0328 mol) were heated at reflux in *n*-BuOH (50 mL) for 16 h. The solution was cooled and filtered, and the crystals were washed with petroleum ether (bp 40–60 °C) (2 × 50 mL) to give 1-*n*-butyl-3-[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]thiourea (3.80 g) (70%), mp 186–188 °C. Anal. ($C_{14}H_{18}N_4S_2$) C, H, N. A stirred mixture of the thiourea (1.22 g, 0.0040 mol), mercury(II) oxide (0.86 g, 0.0040 mol) and 3-(dimethylamino)propylamine (0.82 g, 0.0040 mol) in *n*-BuOH (12 mL) was heated at 60–65 °C for 1.5 h. The mixture was filtered, the solvent was evaporated, and the residue was extracted into 2 N HCl (50 mL). The aqueous solution was washed with $CHCl_3$ and basified with ammonia (0.88 g/mL), and the product was isolated by extraction with $CHCl_3$. Evaporation of the extracts gave an oil, which was converted to a hydrochloride salt and recrystallized from EtOH–Et_2O to give 91 (1.21 g) (63%): mp 177–180 °C; ^1H NMR (DMSO-d_6) δ 2.50 (s, 3 H, Me), 2.77 (d, J = 6 Hz, 6 H,

(13) Russo, F.; Santagati, M.; Alberghina, M. *Farmaco, Ed. Sci.* **1975**, *30*, 1031. Russo, F.; Santagati, M.; Santagati, A. *Farmaco, Ed. Sci.* **1978**, *33*, 26.

NMe_2), 7.3–7.8 (m, 4 H, Ar H), 7.9–8.3 (m, 3 H, NH). Anal. ($C_{19}H_{30}N_6S_2$·2HCl) C, H, N.

Method E. 2-[[5-(2-Methylphenyl)-1,3,4-thiadiazol-2-yl]imino]imidazolidine Hydrochloride (93). A stirred solution of the dithiocarbamate **9** (6.00 g, 0.0213 mol) and ethylenediamine (1.28 g, 0.0213 mol) in *n*-BuOH (54 mL) was heated at reflux for 2 h. The mixture was cooled and filtered, and the product was washed with cold EtOH. Conversion to a hydrochloride salt followed by crystallization from $CHCl_3$–petroleum ether (bp 40–60 °C) gave **93** (3.81 g) (60%): mp 231–232 °C; ^1H NMR (base) ($CDCl_3$) δ 2.60 (s, 3 H, Me), 3.75 (s, 4 H, CH_2CH_2), 7.1–8.2 (m, 6 H, Ar H and NH). Anal. ($C_{12}H_{13}N_5S$·HCl) C, H, N.

1-(2-Aminoethyl)-2-[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]guanidine Dihydrochloride (89). The *N*-acetyl compound **88** (2.60 g, 0.0089 mol) in 6 N HCl (30 mL) was heated at 100 °C for 16 h. The solution was cooled and filtered, and the resultant solid was crystallized from MeOH to give **89** (0.98 g) (34%), mp 208–210 °C. Anal. ($C_{12}H_{16}N_6S$·2HCl) C, H, N.

***N*-Methyl-*N*-[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]-4,5-dihydro-1*H*-imidazol-2-amine (98).** The 2-aminothiadiazole **5** (15.0 g, 0.0784 mol) was added to a stirred mixture[14] of acetic anhydride (90 mL) and formic acid (45 mL) at 0 °C. The mixture was allowed to reach room temperature over 3 h. MeOH (300 mL) was added slowly, and the solution was evaporated to dryness. The residue was slurried with Et_2O, filtered, and dried to give the crude *N*-formyl derivative (13.3 g, 0.0607 mol), which was added in portions to $LiAlH_4$ (6.5 g, 0.1710 mol) in dry Et_2O (130 mL) at room temperature, and the mixture was heated at reflux for 1.5 h. Water was added cautiously to the cooled mixture, and the solids were removed by filtration and washed with THF (50 mL). The combined filtrates were evaporated, and the resultant solid was recrystallized from EtOH to give 2-(methylamino)-5-(2-methylphenyl)-1,3,4-thiadiazole (11.9 g) (74%), mp 106–109 °C. Anal. ($C_{10}H_{11}N_3S$) C, H, N. A portion of this material (4.4 g) was converted to the corresponding *S*-methyl dithiocarbamate by the procedure (method D) described above and then by reaction with ethylenediamine (method E) to the imidazole **98** (0.32 g) (5%): mp 222–224 °C; ^1H NMR (DMSO-d_6) δ 2.50 (s, 3 H, Me), 3.70 (s, 3 H, NMe), 3.80 (s, 4 H, CH_2CH_2), 7.2–7.8 (m, 4 H, Ar H), 9.6–10.0 (br s, 1 H, NH). Anal. ($C_{13}H_{15}N_5S$·HCl·0.5H_2O) C, H, N.

2-[[5-(2-Methylphenyl)-1,3,4-thiadiazol-2-yl]amino]-imidazole Hydrochloride (100). 1-(2,2-Dimethoxyethyl)-2-[5-(2-methylphenyl)-1,3,4-thiadiazol-2-yl]guanidine (12.40 g) was prepared as an oil from cyanamide **7** (8.00 g, 0.0370 mol) and aminoacetaldehyde dimethyl acetal (4.32 g, 0.0410 mol) as described in method B. Without purification, this material was heated with 2 N HCl (150 mL) at 60 °C for 30 min. The solution was cooled, neutralized with aqueous $NaHCO_3$, and extracted with $CHCl_3$. The organic layer was dried and evaporated to give the corresponding aldehyde as a tan solid (4.91 g). A portion of this solid (2.50 g) was heated with concentrated HCl (13 mL) on a steam bath for 1 h. The mixture was cooled and filtered, and the solid was crystallized from EtOH–Et_2O to give **100** (1.10 g) (10%): mp 205–209 °C; ^1H NMR (DMSO-d_6) δ 2.53 (s, 3 H, Me), 7.2–7.7 (m, 6 H, Ar H), 8–10 (v br m, 2 H, NH). Anal. ($C_{12}H_{11}N_5S$·HCl·0.5H_2O) C, H, N.

Pharmacology. The screening procedures in DOCA hypertensive rats and the methods used in the pithed rat experiments were as described previously.[1]

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Registry No. **3** (Ar = Ph), 13373-11-0; **3** (Ar = Me-*o*-C_6H_4), 40642-55-5; **3** (Ar = Me-*m*-C_6H_4), 40642-56-6; **3** (Ar = Me-*p*-C_6H_4), 40288-18-4; **3** (Ar = F-*o*-C_6H_4), 91660-19-4; **3** (Ar = F-*m*-C_6H_4), 91660-20-7; **3** (Ar = F-*p*-C_6H_4), 91660-21-8; **3** (Ar = Cl-*o*-C_6H_4), 36894-93-6; **3** (Ar = Cl-*m*-C_6H_4), 91660-25-2; **3** (Ar = Cl-*p*-C_6H_4), 19430-31-0; **3** (Ar = CF_3-*o*-C_6H_4), 107115-00-4; **3** (Ar = CF_3-*m*-C_6H_4), 113111-41-4; **3** (Ar = CF_3-*p*-C_6H_4), 113111-42-5; **3** (Ar = MeO-*o*-C_6H_4), 40288-19-56; **3** (Ar = MeO-*m*-C_6H_4), 113111-43-6; **3** (Ar = MeO-*p*-C_6H_4), 19430-30-9; **3** (Ar = NO_2-*o*-C_6H_4), 113111-44-7; **3** (Ar = NO_2-*p*-C_6H_4), 19430-32-1; **3** (Ar = Br-*o*-C_6H_4), 113111-45-8; **3** (Ar = I-*o*-C_6H_4), 113111-46-9; **3** (Ar = MeS-*o*-C_6H_4), 112764-35-9; **3** (Ar = SOMe-*o*-C_6H_4), 112764-36-0; **3** (Ar = SOPr-*o*-C_6H_4), 112764-37-1; **3** (Ar = Et-*o*-C_6H_4), 113111-47-0; **3** (Ar = *t*-Bu-*o*-C_6H_4), 113111-48-1; **3** (Ar = PrO-*o*-C_6H_4), 113111-49-2; **3** (Ar = Ph-*o*-C_6H_4), 104071-58-1; **3** (Ar = 2,3-$(Me)_2$-C_6H_4), 113111-50-5; **3** (Ar = 2,4-$(Me)_2$-C_6H_4), 113111-51-6; **3** (Ar = 2,5-$(Me)_2$-C_6H_4), 113111-52-7; **3** (Ar = 2,6-$(Me)_2$-C_6H_4), 113111-53-8; **3** (Ar = 3,4-$(Me)_2$-C_6H_4), 113111-54-9; **3** (Ar = 3,5-$(Me)_2$-C_6H_4), 113111-55-0; **3** (Ar = 2,6-$(Cl)_2$-C_6H_4), 113111-56-1; **3** (Ar = 3,4-$(Cl)_2$-C_6H_4), 113111-57-2; **3** (Ar = 2,6-$(OMe)_2$-C_6H_4), 112764-38-2; **3** (Ar = 3,4-$(OMe)_2$-C_6H_4), 113111-58-3; **3** (Ar = 2-Me,4,5-$(OMe)_2$), 113111-59-4; **3** (Ar = 2-Me-4-F-C_6H_4), 113111-60-7; **3** (Ar = 2-Me-5-F-C_6H_4), 113111-61-8; **3** (Ar = c-C_6H_{11}), 113111-62-9; **3** (Ar = 1-naphthyl), 113111-63-0; **3** (Ar = 2-pyridyl), 76686-93-6; **3** (Ar = 2-furyl), 113111-64-1; **3** (Ar = 2-thienyl), 113111-65-2; **3** (Ar = 3-Me-2-thienyl), 113111-66-3; **5**, 59565-54-7; **5** (thiocarbamate deriv), 113113-21-6; **7**, 113113-23-8; **8**, 113113-22-7; **9**, 113113-54-5; **10**, 110963-11-6; **10**·HCl, 113112-11-1; **11**, 113111-67-4; **11**·HCl, 113112-12-2; **12**·HCl, 113112-13-3; **13**, 113111-69-6; **13**·HCl, 113112-14-4; **14**, 113111-70-9; **14**·HCl, 113112-15-5; **15**, 113111-71-0; **15**·HCl, 113112-16-6; **16**, 113111-72-1; **16**·HCl, 113112-17-7; **17**, 113111-73-2; **17**·HCl, 113112-18-8; **18**, 113111-74-3; **18**·HCl, 113112-19-9; **19**, 113111-75-4; **19**·HCl, 113112-20-2; 20, 107114-98-7; **20**·HCl, 107114-83-0; **21**, 113111-76-5; **21**·HCl, 113112-21-3; **22**, 11311-77-6; **22**·HCl, 113112-22-4; **23**, 113111-78-7; **23**·HCl, 113112-23-5; **24**, 113111-78-7; **24**·HCl, 113112-24-6; **25**, 113111-79-8; **25**·HCl, 113112-25-7; **26**, 113111-80-1; **26**·HCl, 113112-26-8; **27**, 88541-03-1; **27**·HCl, 113112-27-9; **28**, 113111-81-2; **28**·HCl, 113112-28-0; **29**, 113111-82-3; **29**·HCl, 113112-29-1; **30**, 113111-83-4; **30**·HCl, 113112-30-4; **31**, 113111-84-5; **31**·HCl, 113112-31-5; **32**, 113111-85-6; **32**·HCl, 113112-32-6; **33**, 113111-86-7; **34**, 113111-87-8; **35**, 113111-88-9; **35**·HBr, 113112-33-7; **36**, 113111-89-0; **36**·HCl, 113112-34-8; **37**, 113111-90-3; **37**·HCl, 113112-35-9; **38**, 113111-91-4; **38**·2HCl, 113112-36-0; **39**, 113111-92-5; **39**·HCl, 113112-37-1; **40**, 113111-93-6; **40**·HCl, 113112-38-2; **41**, 113111-94-7; **41**·HCl, 113112-39-3; **42**, 113111-95-8; **42**·HCl, 113112-40-6; **43**, 113111-96-9; **43**·HCl, 113112-41-7; **44**, 113111-97-0; **44**·HCl, 113112-42-8; **45**, 113111-98-1; **46**, 113111-99-2; **46**·HCl, 113112-43-9; **47**, 113112-00-8; **48**, 113112-01-9; **48**·HCl, 113112-44-0; **49**, 113112-02-0; **49**·HCl, 113112-45-1; **50**, 113112-03-1; **50**·HCl, 113112-46-2; **51**, 113112-04-2; **51**·HCl, 113112-47-3; **52**, 113112-05-3; **53**, 113112-06-4; **53**·HCl, 113112-48-4; **54**, 113112-07-5; **54**·HCl, 113112-49-5; **55**, 113112-08-6; **55**·HCl, 113112-50-8; **56**, 113112-09-7; **56**·HCl, 113112-51-9; **57**, 113112-10-0; **57**·HCl, 113112-52-0; **58**, 113112-53-1; **59**, 113112-54-2; **59**·HCl, 113112-88-2; **60**, 113112-55-3; **60**·HCl, 113112-89-3; **61**, 113112-56-4; **61**·HCl, 113112-90-6; **62**, 113112-57-5; **62**·HCl, 113112-91-7; **63**, 113112-58-6; **63**·HCl, 113112-92-8; **64**, 113112-59-7; **64**·HCl, 113112-93-9; **65**, 113112-60-0; **65**·HCl, 113112-94-0; **66**, 113112-61-1; **66**·HCl, 113112-95-1; **67**, 113112-62-2; **67**·HCl, 113112-96-2; **68**, 113112-63-3; **68**·HCl, 113112-97-3; **69**, 113112-64-4; **69**·HCl, 113112-98-4; **70**, 113112-65-5; **70**·HCl, 113112-99-5; **71**, 113112-66-6; **71**·HCl, 113112-00-8; **72**, 113112-67-7; **72**·HCl, 113112-01-9; **73**, 113112-68-8; **73**·HCl, 113113-02-3; **74**, 113112-69-9; **74**·HCl, 113113-03-4; **75**, 113112-70-2; **75**·2HCl, 113113-04-5; **76**, 113112-71-3; **76**·HCl, 113113-05-6; **77**, 113112-72-4; **77**·HCl, 113113-06-7; **78**, 113112-73-5; **78**·HCl, 113113-07-8; **79**, 113112-74-6; **79**·HCl, 113113-08-9; **80**, 113112-75-7; **80**·HCl, 113113-09-0; **81**, 113112-76-8; **81**·HCl, 113113-10-3; **82**, 113112-77-9; **82**·HCl, 113113-11-4; **83**, 113112-78-0; **83**·HCl, 113113-12-5; **84**, 113112-79-1; **84**·HCl, 113112-80-4; **85**, 113112-80-4; **85**·HCl, 113113-14-7; **86**, 113112-81-5; **86**·HCl, 113113-15-8; **87**, 113112-82-6; **87**·HCl, 113113-16-9; **88**, 113112-83-7; **89**, 113112-84-8; **89**·HCl, 113113-17-0; **90**, 113112-85-9; **90**·2HCl, 113113-18-1; **91**, 113112-86-0; **91**·2HCl, 113113-19-2; **92**, 113112-87-1; **92**·HCl, 113113-20-5; **93**, 113113-35-2; **94**, 113113-27-2; **94**·HCl, 113113-36-3; **95**, 113113-28-3; **95**·HCl, 113113-37-4; **96**, 113113-29-4; **96**·HCl, 113113-38-5; **97**, 113113-30-7; **97**·HCl, 113113-39-6; **98**, 113113-31-8; **98**·HCl, 113113-40-9; **99**, 113113-32-9; **99**·HCl, 113113-41-0; **100**, 113113-33-0; **100**·HCl, 113113-42-1; **101**, 113113-34-1; **101**·HCl, 113113-43-2; $(H_2N)_2$=NH, 113-00-8; H_2NC(=NH)NHMe, 471-29-4; H_2NC(=NH)NMe_2, 6145-42-2; MeNHC(=NH)NHMe,

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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

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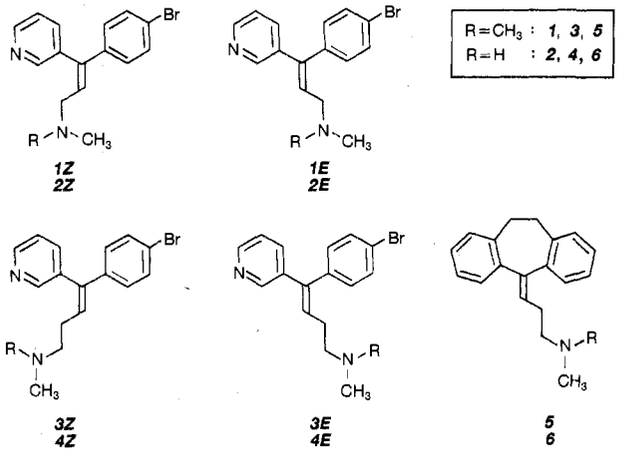
A number of tertiary and secondary homoallylic amines, i.e. (*Z*)- and (*E*)-4-(4-bromophenyl)-4-(3-pyridyl)-3-buten-1-ylamines, were synthesized in diastereomerically pure forms. The compounds were evaluated as neuronal norepinephrine (NE) and serotonin (5-HT) uptake inhibitors under in vitro and ex vivo conditions and compared with the tricyclics amitriptyline and nortriptyline having homoallylic side chains and with the corresponding diastereomers in the zimeldine series having allylic side chains. The *Z* isomers of the new homoallylic derivatives (**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,

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



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

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