Antihypertensive Thiadiazoles. 1. Synthesis of Some 2-Aryl-5-hydrazino-1,3,4-thiadiazoles with Vasodilator Activity

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Some 2-aryl-5-hydrazino-1,3,4-thiadiazoles have been synthesized and screened for antihypertensive activity. In general, compounds with a 2-substituted phenyl ring had higher activity than their 3- or 4-substituted counterparts or those containing heteroaryl groups. The 2-methylphenyl and 2-ethylphenyl derivatives **7** and **18** were the most potent members of the series. Preliminary studies indicated that the hypotensive action of these compounds was due to a direct relaxant effect on vascular smooth muscle.

The vasodilator hydralazine[1] is an effective antihypertensive agent that has been used in combination with β-adrenoreceptor antagonists[2,3] or in triple therapy[2,4] with a β-adrenoreceptor antagonist and a diuretic. At the low doses used in these latter therapeutic regimes, the relatively high incidence of side effects, particularly the serious lupus erythematosus-like syndrome,[5] seen with hydralazine alone, is minimized. The search for safer vasodilators of the hydralazine type led to the discovery of antihypertensive activity in related 3-hydrazinopyridazines of general structure **2**. Groups in the 6-position have included alkyl,[6]

aryl,[7] heteroaryl,[8] and, in some particularly potent compounds, secondary amino substituents.[9] We were interested in determining whether 2-aryl-5-hydrazino-1,3,4-thiadiazoles **3**, in which the heteroaromatic ring is bioisosteric with the pyridazine ring in **2**, would retain vasodilator activity.

The 5-phenyl derivative **6** had already been described,[10,11] and some other substituted phenyl analogues[12,13] were disclosed during the course of this work, but there were no reports of these compounds possessing antihypertensive properties. Resynthesis and pharmacological evaluation of **6** revealed an interesting level of antihypertensive activity, and our investigations into structure–activity relationships in this series are now reported. Results on four compounds in this series (**7, 10, 24,** and **26**) have been reported previously.[14]

Chemistry

The 2-amino-5-aryl-1,3,4-thiadiazoles **4** (Scheme I) were obtained by modifications of established procedures from arylthiosemicarbazones[15] or aroylthiosemicarbazides[16] or by direct cyclization of a carboxylic acid and thiosemicarbazide in polyphosphoric acid[17] (methods A–C). Diazotization of **4** in hydrochloric acid, either with[18] or without[11] copper catalysis, gave the 2-chloro compounds **5**. Treatment with hydrazine hydrate[11] completed the synthesis. During diazotization of the 2-(methylthio)phenyl compound **4a**, partial oxidation[19] occurred to give a mixture of **5a** and the corresponding sulfoxide **5b**. In a similar reaction, on the 2-(*n*-propylthio)phenyl analogue **4b** only

Scheme I[a]

5a, R=2-SMe
b, R=2-SOMe
c, R=2-SOCH₂CH₂Me
d, R=2,6-(OMe)₂
e, R=2,6(OMe)₂-3-Cl

4a, R=2-SMe
b, R=2-SCH₂CH₂Me
c, R=2,6-(OMe)₂

[a] (i) FeCl₃; (ii) PPA; (iii) PPA/H₂NNHCSNH₂; (iv) NaNO₂/HCl/Cu; (v) N₂H₄·H₂O.

the sulfoxide **5c** was obtained. Diazotization of the 2,6-dimethoxyphenyl compound **4c** in concentrated hydro-

(1) Druey, J.; Marxer, J. *J. Med. Pharm. Chem.* **1959**, *1*, 1. Druey, J.; Tripod, J. *Antihypertensive Agents*; Academic: New York, 1967; pp 223–262.
(2) Zacest, R.; Gilmore, E.; Koch-Weser, J. *N. Engl. J. Med.* **1972**, *286*, 617.
(3) Pape, J. *Acta. Med. Scand., Suppl.* **1974**, *554*, 55. Koch-Weser, J. *N. Engl. J. Med.* **1976**, *295*, 320.
(4) Gottlieb, T. B.; Katz, F. H.; Chidsey, C. A. *Circulation* **1972**, *45*, 571. Forrest, W. A. *Br. J. Clin. Pract.* **1978**, *32*, 326.
(5) Perry, H. M., Jr. *Am. J. Med.* **1973**, *54*, 58.
(6) Dixon, S.; Wiggins, L. F. *J. Chem. Soc.* **1950**, 3236.
(7) Hartmann, M.; Druey, J. U.S. Pat. 2 484 029, 1949.
(8) Szilagyi, G.; Kasztreiner, E.; Tardos, L.; Jaszlits, L.; Kosa, E.; Cseh, G.; Tolnay, P.; Kovacs-Szabo, I. *Eur. J. Med. Chem.* **1979**, *14*, 439.
(9) Pifferi, G.; Parravicini, F.; Carpi, C.; Dorigotti, L. *J. Med. Chem.* **1975**, *18*, 741. Parravicini, F.; Scarpitta, G.; Dorigotti, L.; Pifferi, G. *Farmaco, Ed. Sci.* **1979**, *34*, 299.
(10) Fujii, K.; Yoshikawa, H.; Yuasa, M. *J. Pharm. Soc. Jpn.* **1954**, *74*, 1056.
(11) Potts, K. T.; Huseby, R. M. *J. Org. Chem.* **1966**, *31*, 3528.
(12) Shafiee, A.; Lalezari, I.; Mirrashed, M. *J. Heterocycl. Chem.* **1976**, *13*, 117.
(13) Shanseldine, S. A.; Jawad, F. H.; Mahmoud, N. F. *Pharmazie* **1984**, *39*, 101.
(14) Chapleo, C. B.; Myers, M.; Myers, P. L.; Saville, J. F.; Smith, A. C. B.; Stillings, M. R.; Tulloch, I. F.; Walter, D. S.; Welbourn, A. P. *J. Med. Chem.* **1986**, *29*, 2273.
(15) Rao, V. R.; Srinivasan, V. R. *Indian J. Chem.* **1970**, *8*, 509.
(16) Hoggarth, E. *J. Chem. Soc.* **1949**, 1163.

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Table I

no.	R	method	mp, °C	recrystn solvent	yield, %	formula[a]	reduction[b] in MABP,[c,d] % ± SEM
6	H[e]	A	201–203	EtOH	45	$C_8H_8N_4S \cdot HCl$	42 ± 3
7	2-Me[f]	C	169–172	MeOH–Et$_2$O	47	$C_9H_{10}N_4S \cdot HCl$	48 ± 2 (50 mg/kg, po)
							33 ± 2 (25 mg/kg, po)
8	3-Me	B	152–155	EtOH–Et$_2$O	62	$C_9H_{10}N_4S \cdot HCl$	29 ± 12
9	4-Me[f]	A	176–180	EtOH–Et$_2$O	32	$C_9H_{10}N_4S \cdot HCl$	28 ± 1
10	2-Cl[f]	C	174–176	EtOH	45	$C_8H_7ClN_4S \cdot HCl$	21 ± 2
11	3-Cl[f]	A	172 dec	MeOH–Et$_2$O	51	$C_8H_7ClN_4S \cdot HCl$	20 ± 5
12	4-Cl[f]	A	185–190	MeOH	28	$C_8H_7ClN_4S \cdot HCl$	28 ± 6 (100 mg/kg, ip)
13	2-OMe	A	177–180	EtOH	56	$C_9H_{10}N_4OS \cdot HCl \cdot 0.5H_2O$	46 ± 4
							39 ± 3 (50 mg/kg, po)
14	3-OMe[f,g]	A	176–180	MeOH	60	$C_9H_{10}N_4OS \cdot HCl$	18 ± 2
15	2-CF$_3$	B	179–181	EtOH–Et$_2$O	15	$C_9H_7F_3N_4S \cdot HCl$	49 ± 5
							33 ± 6 (50 mg/kg, po)
16	3-CF$_3$	A	160–161	EtOH	24	$C_9H_7F_3N_4S \cdot HCl^h$	21 ± 2
17	4-CF$_3$	B	230–231	MeOH–Et$_2$O	23	$C_9H_7F_3N_4S \cdot HCl$	21 ± 3
18	2-Et	B	135–138	EtOH–Et$_2$O	37	$C_{10}H_{12}N_4S \cdot HCl$	54 ± 3 (50 mg/kg, po)
							42 ± 3 (25 mg/kg, po)
19	2-t-Bu	B	155–157	EtOH–Et$_2$O	16	$C_{12}H_{16}N_4S$	58 ± 3
20	2-F	A	231–232	EtOH–Et$_2$O	52	$C_8H_7FN_4S \cdot HCl$	31 ± 4
21	2-Br	A	158–161	MeOH–Et$_2$O	69	$C_8H_7BrN_4S \cdot HCl$	48 ± 3
22	2-I	B	157–159	EtOH–Et$_2$O	40	$C_8H_7IN_4S \cdot HCl$	58 ± 2
							24 ± 4 (50 mg/kg, po)
23	2-O-n-Pr	A	146–150	EtOH–Et$_2$O	25	$C_{11}H_{14}N_4OS \cdot HCl$	46 ± 4
24	2-O-n-hexyl	A	163–166	i-PrOH	34	$C_{14}H_{20}N_4OS \cdot HCl$	IA[i]
25	2-NO$_2$	A	166–172	MeOH–Et$_2$O	41	$C_8H_7N_5SO_2 \cdot HCl$	26 ± 4
26	2-Ph	A	276–279	EtOH	29	$C_{14}H_{12}N_4S \cdot HCl$	18 ± 1
27	2-SMe	B	160–162	MeOH–Et$_2$O	39	$C_9H_{10}N_4S_2 \cdot HCl$	41 ± 4
28	2-SOMe	B[j]	190–192	MeOH–Et$_2$O	64	$C_9H_{10}N_4S_2O \cdot HCl$	45 ± 4 (50 mg/kg, po)
							31 ± 4 (25 mg/kg, po)
29	2-SO-n-Pr	B[j]	163–166	MeOH–Et$_2$O	45	$C_{11}H_{14}N_4OS_2 \cdot HCl$	48 ± 4
30	3-OH	j	208–209	EtOH	19	$C_8H_8N_4OS \cdot HCl$	16 ± 5
31	2,3-Me$_2$	A	161–164	MeOH	54	$C_{10}H_{12}N_4S \cdot HCl$	50 ± 6
32	2,4-Me$_2$	A	146–150	EtOH	21	$C_{10}H_{12}N_4S \cdot HCl$	61 ± 2
33	2,5-Me$_2$	B	171–174	EtOH	31	$C_{10}H_{12}N_4S \cdot HCl$	50 ± 5
34	2,6-Me$_2$	A	196–199	EtOH–petroleum ether	22	$C_{10}H_{12}N_4S \cdot HCl^k$	54 ± 1
35	3,4-Me$_2$	B	155–157	EtOH–Et$_2$O	21	$C_{10}H_{12}N_4S \cdot HCl$	22 ± 7
36	3,5-Me$_2$	B	207–208	EtOH	34	$C_{10}H_{12}N_4S \cdot HCl^l$	18 ± 2
37	2,6-Cl$_2$	A	185–187	EtOH	56	$C_8H_6Cl_2N_4S$	50 ± 3
38	3,4-Cl$_2$	A	269–270	EtOH	53	$C_8H_6Cl_2N_4S \cdot HCl$	17 ± 1
39	2,6-(OMe)$_2$	B	188–191	EtOH–Et$_2$O	38	$C_{10}H_{12}N_4O_2S \cdot HCl$	33 ± 1
40	3,4-(OMe)$_2$	A	194–196	MeOH	46	$C_{10}H_{12}N_4O_2S \cdot HCl$	24 ± 2 (100 mg/kg, ip)
41	2-Me-4-F	C	175–179	EtOH	48	$C_9H_9FN_4S \cdot HCl$	58 ± 4
42	2-Me-5-F	A	165–167	EtOH	21	$C_9H_9FN_4S \cdot HCl$	63 ± 3
43	2,6-(OMe)$_2$-3-Cl	B[j]	113–115	EtOH	21	$C_{10}H_{11}ClN_4O_2S \cdot HCl$	53 ± 4
hydralazine							39 ± 2 (5 mg/kg, po)
minoxidil							42 ± 3 (10 mg/kg, po)

[a] Elemental analyses for C, H, N were with ±0.4% of the calculated values except where otherwise indicated. [b] Maximum percentage reduction, compared to the mean of two pretreatment controls, in MABP in DOCA hypertensive rats (n = 3–5). [c] Mean arterial blood pressure = diastolic blood pressure plus one-third pulse pressure. [d] Results refer to an oral dose of 100 mg/kg unless otherwise indicated. [e] The base has previously been described ref 10 and 11. [f] As e, ref 12. [g] As e, ref 13. [h] N: calcd 18.88, found 19.30. [i] Inactive; maximum percentage fall in MABP <10%. [j] See the Experimental Section. [k] N: calcd, 21.82; found, 22.32. [l] C: calcd, 46.78; found, 47.21.

chloric acid in the presence of metallic copper resulted in some ring chlorination[20] to give approximately equal amounts of the expected product **5d** and the 3-chloro analogue **5e**.

Results and Discussion

The effects of the thiadiazole hydrazines on mean arterial blood pressure (MABP) and heart rate were monitored in metacorticoid (DOCA) hypertensive rats at a
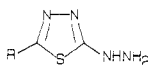
(17) We are indebted to J. A. Davis (Reckitt & Colman) for the particular experimental procedure used.
(18) Alemagna, A.; Bacchetti, T. *Tetrahedron* **1968**, *24*, 3209.
(19) Gilman, H.; Swayampati, R. *J. Am. Chem. Soc.* **1956**, *78*, 2163.
(20) Ware, J. C.; Borchert, E. E. *J. Org. Chem.* **1961**, *26*, 2263. Nonhebel, D. C. *J. Chem. Soc.* **1963**, 1217.

standard oral dose of 100 mg/kg. The results, expressed as percentage reductions in MABP, compared with pretreatment controls are shown in Tables I and II. The majority of the hydrazines caused significant reductions in blood pressure, but the effects on heart rate (not shown) were generally quite small. Usually, a slight tachycardia was observed, but this was not dose related. Hydralazine, though producing increases in heart rate in normotensive rats,[1] also had little effect on heart rate in DOCA hypertensive rats.

In examining structure–activity relationships (SAR) in this series, it was quickly evident that substitution in the 2-position, as opposed to the 3- or 4-positions of the phenyl ring, resulted in greater antihypertensive activity. For example, compare **7** with **8** and **9** and **15** with **16** and **17**. The 2-chlorophenyl derivative **10** which had a similar level

Table II

no.	R	method	mp, °C	recrystn solvent	yield, %	formula[a]	reduction[b] in MABP,[c,d] % ± SEM
44	2-thienyl	A	204–207	MeOH	43	$C_6H_6N_4S_2 \cdot HCl$	35 ± 9
45	3-thienyl	A	177–179	EtOH	61	$C_6H_6N_4S_2 \cdot HCl$	33 ± 1
46	3-methylthien-2-yl	A	172–175	MeOH	35	$C_7H_8N_4S_2 \cdot HCl$	48 ± 10
47	2-furyl	A	167–169	MeOH	62	$C_6H_6N_4OS \cdot HCl$	39 ± 4
48	2-pyridyl	A	214–220	MeOH–Et_2O	30	$C_7H_7N_5S \cdot HCl$	21 ± 2
49	1-naphthyl	A	170–173	MeOH	37	$C_{12}H_{10}N_4S \cdot HCl$	26 ± 7

[a-d] See corresponding footnotes in Table I.

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

treatment	electrical stimulation, Hz			noradrenaline, μg/kg, iv			angiotensin μg/kg, iv		
	1	3	6	0.1	0.3	1.0	0.03	0.1	0.3
control[b]	52 ± 4	77 ± 3	93 ± 3	40 ± 8	54 ± 5	75 ± 5	33 ± 3	52 ± 4	77 ± 4
7[c]	16 ± 2	32 ± 4	41 ± 3	10 ± 1	16 ± 1	29 ± 1	12 ± 1	28 ± 4	50 ± 3
control	49 ± 5	64 ± 3	77 ± 3	24 ± 2	44 ± 2	67 ± 2	25 ± 1	40 ± 2	54 ± 3
18[d]	14 ± 2	25 ± 2	32 ± 3	8 ± 1	14 ± 1	22 ± 1	2 ± 1	6 ± 2	25 ± 3
control	52 ± 4	77 ± 3	93 ± 3	40 ± 8	54 ± 5	75 ± 5	33 ± 3	52 ± 4	77 ± 4
28[e]	19 ± 4	34 ± 6	47 ± 7	6 ± 1	10 ± 1	21 ± 3	4 ± 2	11 ± 2	29 ± 5
control	52 ± 4	77 ± 3	93 ± 3	40 ± 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
control	33 ± 5	58 ± 5	67 ± 5	18 ± 1	34 ± 2	59 ± 3	12 ± 1	31 ± 3	50 ± 3
minoxidil[g]	9 ± 2	25 ± 4	31 ± 4	10 ± 1	25 ± 2	45 ± 3	6 ± 1	13 ± 3	25 ± 4
control	52 ± 4	77 ± 3	93 ± 3	40 ± 8	54 ± 5	75 ± 5	33 ± 3	52 ± 4	77 ± 4
prazosin[h]	18 ± 3	26 ± 2	31 ± 2	23 ± 3	32 ± 2	49 ± 3	30 ± 3	45 ± 3	67 ± 4

[a] See the Experimental Section for general method. [b] Isotonic saline, ip. [c] A dose of 25 mg/kg, ip, was administered to groups of five rats 2 h prior to the pithing procedure. [d] As footnote c at 1 h. [e] As footnote c, 50 mg/kg, ip, at 1 h. [f] As footnote c, 5 mg/kg, ip, at 1 h. [g] As footnote c, 20 mg/kg, ip, at 1 h. [h] As footnote c, 1 mg/kg, at 1 h.

of activity to the 3-substituted phenyl compound 11 was, however, an exception. Examination of a range of 2-substituted phenyl compounds showed that the majority produced reductions in MABP that were greater than, or comparable to, those seen with the unsubstituted phenyl derivative 6. The exceptions were those containing the *n*-hexyl and phenyl groups (24 and 26), the lower halogens (10 and 20), and a nitro group (25). The remainder of the 2-substituted phenyl compounds (Table I) produced substantial falls in MABP (41–58%), and with three of these (7, 18, and 28), reductions of this magnitude occurred at half the standard dose. A study (not shown) in which these three compounds were compared in DOCA hypertensive rats, at a minimum of three dose levels producing reductions in MABP of 20–70%, the relative potencies were in the order 18 > 7 > 28. Typically, 2 h after a 50 mg/kg oral dose of 18 to these animals, reductions in blood pressure of approximately 50% were observed that persisted at this level for a further 6 h and were still significantly below control values 24 h after dosing.

Dimethylphenyl compounds with at least one ortho substituent (31–34) retained considerable antihypertensive activity, but, as would be predicted from the monosubstituted analogues, the 3,4- and 3,5-dimethyl compounds 35 and 36 were much less active. The overriding influence of a 2-methyl group in disubstituted phenyl compounds was also evident in derivatives (41 and 42) with fluorine in the 4- or 5-position. Results seen with some other disubstituted and trisubstituted phenyl compounds were not readily explained. The 2,6-dichlorophenyl compound 37 showed enhanced antihypertensive activity compared to the monosubstituted derivative 10, but in the corresponding pair of methoxy-substituted analogues 13 and 39, 2,6-disubstitution lowered activity. Furthermore, in the 2,6-dimethoxyphenyl compound 43 with an additional

3-chloro group, activity was restored.

Of the compounds examined that had naphthyl or heteroaryl groups in the 5-position of the thiadiazole ring (Table II), the most effective was the 3-methylthienyl derivative 46, a close analogue of the potent 2-methylphenyl compound 7.

Some preliminary studies on the mechanism of the antihypertensive action of these thiadiazole hydrazines were performed in pithed rat preparations. In this model, the effects of some of the more potent compounds (7, 18 and 28) on pressor responses evoked either by stimulation of the entire sympathetic outflow or by intravenous injections of noradrenaline or angiotensin were examined. The results compared with those for hydralazine, minoxidil, and the α_1-adrenoreceptor antagonist prazosin[21] are shown in Table III. The thiadiazoles all produced a significant, nonspecific suppression of pressor responses, which is characteristic of direct-acting vasodilators of the hydralazine type.[22] In contrast, prazosin selectively antagonized the sympathetic stimulation and nonadrenaline responses without affecting the pressor effects of angiotensin.

The persistent hypotensive effect, lasting for at least 24 h, produced by the more potent of these thiadiazole hydrazines, has already been noted. In this regard, it was of interest that 7 was found to localize with high affinity in arterial tissue over this time period. Metabolic studies[23]

(21) Cambridge, D.; Davey, M. J.; Massingham, R. *Med. J. Aust.* **1977**, *2* (Suppl. 1), 2. Doxey, J. C.; Roach, A. G.; Smith, C. F. C. *Br. J. Pharmacol.* **1983**, *78*, 489.

(22) Rubin, A. A.; Roth, F. E.; Taylor, R. M.; Rosenkilde, H. *J. Pharmacol. Exp. Ther.* **1972**, *136*, 344.

(23) Bartlett, A. J.; Havler, M. E.; Rance, M. J. (Reckitt & Colman), unpublished results.

in rats with [$^{14}C_5$]-7 (20 mg/kg, po) showed that the level of radioactivity present in the aorta was approximately 4 times higher than peak plasma values (0.5–1 h) and that the amount of drug-related material (of unknown composition), in the aorta, remained at this level for at least 24 h. Some of this material, located in the elastic elements of blood vessel walls, may be associated with the observed hypotensive effect. However, the further finding that amounts of radioactivity (2–1.5 times peak plasma levels) persisted in the aorta at times (2–7 days) when cardiovascular parameters had returned to normal indicated that some part of this bound material had no relevance to the antihypertensive action of 7. Similar results have been reported[24] for [^{14}C]hydralazine; in rats the half-life of radioactivity in blood vessel walls was greater than 30 h.

The acute toxicity of the 2-methylphenyl compound 7, determined in male rats following oral dosing, was quite high (LD_{50} = 120 mg/kg). Anoxia produced by profound reductions in blood pressure was primarily responsible for the observed fatalities in this study.

Conclusion

Structure–activity studies in these thiadiazole hydrazines highlighted several 2-substituted phenyl derivatives (7, 18 and 28), which produced prolonged falls in blood pressure in DOCA hypertensive rats with only a slight, non dose related tachycardia. From studies in pithed rat preparations, it was concluded that, like hydralazine and minoxidil, these compounds exerted their hypotensive effects by a direct relaxant action on vascular smooth muscle. The 2-ethylphenyl derivative 18 was approximately 5 times less potent than hydralazine in DOCA hypertensive rats. The relatively high oral toxicity of the 2-methylphenyl compound 7 coupled with concern over the persisting levels of drug-related material in arterial tissue discouraged further work on these hydrazine derivatives.

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.

2-Amino-5-aryl-1,3,4-thiadiazoles (4). Method A. The procedure was a slight modification of that used by Rao and Srinivason.[15] An arylthiosemicarbazone (0.1 mol) and $FeCl_3 \cdot 6H_2O$ (0.4 mol) in EtOH (1 L) were heated and stirred at reflux for 1–2 h. The solvent was evaporated, the residue was dissolved in the minimum amount of concentrated HCl (300–350 mL), and water (0.75–1 L) was added. The precipitate of the hydrochloride salt was suspended in water (100 mL), basified with excess NH_3 (0.88 g/mL), filtered, and dried. The 2-aminothiadiazole 4 at this stage was generally satisfactory for further reactions, but where necessary purification was by crystallization from EtOH or MeOH.

Method B. An aroylthiosemicarbazide[16] (0.1 mol) was added in portions over 0.5 h to vigorously stirred polyphosphoric acid at 100 °C. The mixture was kept at this temperature for a further 0.5 h and cooled, water/ice was added, and the mixture was finally basified with NH_3 (0.88 g/mL). The solids isolated by filtration were washed with water and air-dried to give the 2-aminothiadiazole 4, which was purified, if required, as in method A.

Method C.[17] A finely ground mixture of the aryl carboxylic acid (0.1 mol) and thiosemicarbazide (0.1 mol) was added in portions over 0.5 h to polyphosphoric acid (10 times the weight

of carboxylic acid) at 80–90 °C, and the mixture was stirred at this temperature for 2–4 h. The product was isolated as in method B.

2-Chloro-5-aryl-1,3,4-thiadiazoles (5). Two slightly differing procedures, exemplified by the general method below and that for the precursors to compounds 27 and 28, were used. In a similar manner to that described by Alemagna and Bacchetti,[18] a stirred suspension of 4 (0.05 mol) in a mixture of glacial HOAC (150 mL) and concentrated HCl (30 mL) with copper turnings (0.1 times the weight of 4) was cooled to 15 °C, and a solution of sodium nitrite (0.051 5 mol) in water (10 mL) was added over 0.5 h. The mixture was kept at 15–20 °C for a further 2–4 h, poured into water, and extracted with $CHCl_3$ (three times). The combined extracts were washed with $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated to give crude 5. If necessary, purification was by passage through a short silica gel column with either $CHCl_3$ or Et_2O–petroleum ether (bp 40–60°C) as eluants.

2-Aryl-5-hydrazino-1,3,4-thiadiazoles (3). In a slight modification to the procedure of Potts and Huseby,[11] a solution of a 2-chlorothiadiazole 5 (0.025 mol) and hydrazine hydrate (0.075 mol) in EtOH (50 mL) was heated at reflux for 2–4 h. The solvent was evaporated, water was added, and the product was isolated by filtration, converted to the HCl salt, and crystallized.

2-Chloro-5-[2-(methylthio)phenyl]-1,3,4-thiadiazole (5a) and 2-Chloro-5-[2-(methylsulfinyl)phenyl]-1,3,4-thiadiazole (5b). The 2-aminothiadiazole 4a (15.0 g, 0.067 mol) in concentrated HCl (336 mL) at −25 °C was treated dropwise with sodium nitrite (15.45 g, 0.224 mol) in water (56 mL) over 3 h.[11] After being stirred at this temperature for an additional 4 h, the mixture was allowed to attain room temperature overnight and finally heated on a steam bath for 15 min. The product was extracted into $CHCl_3$. The organic phase was separated, washed with water, dried (Na_2SO_4), and evaporated to give a yellow oil (14.2 g). Chromatography on silica gel (500 g) with $CHCl_3$ as eluant gave the methylthio derivative 5a (3.15 g, 19%). A sample crystallized from Et_2O had mp 51–52 °C: ^1H NMR ($CDCl_3$) δ 2.50 (3 H, s, Me), 7.2–7.7 (m, 3 H, Ar H), 8.0–8.3 (m, 1 H, Ar H). Anal. ($C_9H_7ClN_2S_2$) C, H, N. Further elution gave the sulfoxide 5b (9.0 g, 51%); mp 96–98 °C; ^1H NMR ($CDCl_3$) δ 2.97 (s, 3 H, SOMe), 7.6–8.0 (m, 3 H, Ar H), 8.3–8.5 (m, 1 H, Ar H). Anal. (C_9H_7-$ClON_2S_2$) C, H, N. Conversion to the corresponding hydrazines (27, 28) was by the procedure described in the general methods.

2-Chloro-5-(2,6-dimethoxyphenyl)-1,3,4-thiadiazole (5d) and 2-Chloro-5-(3-chloro-2,6-dimethoxyphenyl)-1,3,4-thiadiazole (5e). Diazotization of the amine 4c (14.0 g, 0.059 mol) via the method for compounds 27 and 28 gave a red oil (19.5 g), which was chromatographed on silica gel (300 g). Elution with $CHCl_3$ gave the 2-chlorothiadiazole 5e (4.1 g, 24%). A sample crystallized from EtOH had mp 117–118 °C: ^1H NMR ($CDCl_3$) δ 3.83 (s, 6 H, OMe), 6.95 (d, J = 9 Hz, 1 H, Ar H), 7.50 (d, J = 9 Hz, 1 H, Ar H). Anal. ($C_{10}H_8Cl_2N_2O_2S$) C, H, N. Further elution gave a yellow solid (4.4 g), which was crystallized from EtOH to give 5d (3.2 g, 21%); mp 120–122 °C; ^1H NMR ($CDCl_3$) δ 3.87 (s, 6 H, OMe), 6.16–6.86 (m, 3 H, Ar H), 7.16–7.63 (m, 1 H, Ar H). Anal. ($C_{10}H_9ClN_2O_2S$) C, H, N. Conversion to the corresponding hydrazines 39 and 43 was by the general method above.

2-Hydrazino-5-(3-hydroxyphenyl)-1,3,4-thiadiazole Hydrochloride (30). The 3-methoxyphenyl derivative 14 (1.40 g, 0.006 3 mol) (free base) was added in portions over 10 min to a solution of BBr_3 (9.48 g, 0.037 8 mol) in dry CH_2Cl_2 (75 mL) at room temperature. After an additional 72 h, the mixture was poured carefully into water, and the crude hydrobromide salt was obtained by filtration. The solid was suspended in stirred $NaHCO_3$ solution, filtered, washed with water, dried, converted to a hydrochloride salt, and recrystallized from EtOH to give 30 (0.45 g, 27%), mp 208–209 °C. Anal. ($C_8H_8N_4OS \cdot HCl$) C, H, N.

Pharmacology. Antihypertensive Screening: Metacorticoid (DOCA) Hypertensive Rats. Metacorticoid (DOCA) hypertension was induced in male, Sprague–Dawley rats weighing 80–110 g by a modification of the method of Stanton and White.[25] Blood pressure was recorded from aortic catheters implanted under halothane anesthesia by the technique of Weeks and

(24) Wagner, J.; Hedwall, P. R. *Recent Advances in Hypertension*; Milliez, P., Safar, M., Eds.; Boehringer: Ingelheim, 1975; p 331.

(25) Stanton, H. C.; White, J. B. *Arch. Int. Pharmacodyn. Ther.* **1965**, *154*, 351.

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.

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$_2$CH$_2$Me), 112764-57-5; i (R = 2,6-(OMe)$_2$), 112764-58-6; ii (R = 2-SMe), 112764-59-7; ii (R = 2-SCH$_2$CH$_2$Me), 112764-60-0; ii (R = 2,6-(OMe)$_2$), 112764-61-1; iii (R = 2-SMe), 3724-10-5; iii (R = 2-SCH$_2$CH$_2$Me), 21213-10-5; iii (R = 2,6-(OMe)$_2$), 1466-76-8; FeCl$_3$, 7705-08-0.

(26) Weeks, J. R.; Jones, J. A. Proc. Soc. Exp. Biol. Med. 1960, 104, 646.

(27) Gillespie, J. S.; Muir, T. C. Br. J. Pharmacol. Chemother. 1967, 30, 78.

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
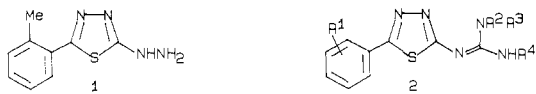
groups have frequently been found to produce antihypertensive effects, in other series, through a number of modes of action, including adrenergic neurone blockade,[2] vasodilation,[3] α_2-adrenoreceptor agonism,[4] and unclassified mechanisms.[5] Some of the unsubstituted guanidinothiadiazoles 4 (Scheme I), though generally less potent

Scheme I[a]
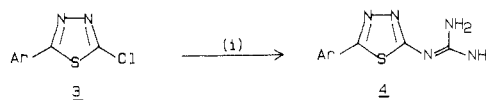
[a] (i) [NH$_2$C(=NH)NH$_2$]$_2$·H$_2$CO$_3$/K$_2$CO$_3$/dioxane.

than the hydrazines (1), retained a similar vasodilator profile, but the length of action was deemed too short.

(1) Turner, S.; Myers, M.; Gadie, B.; Nelson, A. S.; Pape, R.; Saville, J. F.; Doxey, J. C.; Berridge, T. L. J. Med. Chem., preceding paper in this issue.

(2) Durant, G. J.; Roe, A. M.; Green, A. L. Progress in Medicinal Chemistry; Butterworth: London, 1970; p 124. Grobecker, H.; Roizen, M. F.; Jacobowitz, D. M.; Kopin, I. J. Eur. J. Pharmacol. 1977, 46, 125. Reiterer, V. W.; Czitober, H. Arzneim.-Forsch. 1977, 27, 2163.

(3) Gadekar, J.; Nibi, S.; Cohen, E. J. Med. Chem. 1968, 11, 811. Petersen, H. J.; Nielsen, C. K.; Arrigoni-Martelli, E. J. Med. Chem. 1978, 21, 773.

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