(dalamid) for sites on brain membranes. Membranes were incubated for 10 in at 37 °C with [^{3}H]dalamid in the presence (or absence) of competing compoundin 10 mM Tris·HCl, pH 7.5. At the end of the incubation, the samples (0.5 mL) were cooled to 4 °C and passed through columns of Sephadex G-25 (PD-10, Pharmacia). The columns were eluted with four aliquots (1 mL) of Tris buffer directly into scintillation vials. After addition of 12 mL of Aquasolve (New England Nuclear Co.), the radioactivity was monitored by scintillation counting. Unbound radioactivity is retained by the columns under these conditions. After use, columns were washed with 6 M urea and regenerated with Tris buffer.

Adenylate cyclase activity of NG108-15 membranes was measured by assaying the conversion of [α-^{32}P]ATP to cyclic AMP during a 10-min incubation at 37 °C, as previously described.[20]

All experiments with eseroline were performed with freshly prepared solutions that were used within 1 h of preparation. Control experiments showed that, under these conditions, the addition of an equivalent concentration of ascorbic acid had no effect on the potency of eseroline in binding assays.

Acknowledgment. We thank Drs. M. D. Aceto and L. S. Harris (Medical College of Virginia, Virginia Commonwealth University, Richmond, VA) for the data from the TF, PPQ, and TFA assays. These assays were carried out under the auspices of the Committee on Problems of Drug Dependence. We thank Mariena V. Mattson from our laboratory for the screening of the various compounds mentioned. We also thank Dr. Bernhard Witkop for his encouragement and support in this study.

Registry No. (+)-1, 104069-10-5; (-)-1, 104069-11-6; (-)-2, 6785-93-9; (-)-2·H_2SO_4, 104015-27-2; (+)-3, 104069-12-7; (-)-3, 65166-97-4; (+)-4, 29347-15-7; (+)-4·H_2SO_4, 104015-28-3; (-)-4, 469-22-7; (-)-4·H_2SO_4, 104015-29-4; (+)-7, 104015-30-7; (-)-8, 104015-32-9; (-)-8·HCl, 104015-31-8; 9, 18455-27-1; (-)-10, 104034-13-1; adenylate cyclase, 9012-42-4.

Substituted 1,3,4-Thiadiazoles with Anticonvulsant Activity. 1. Hydrazines

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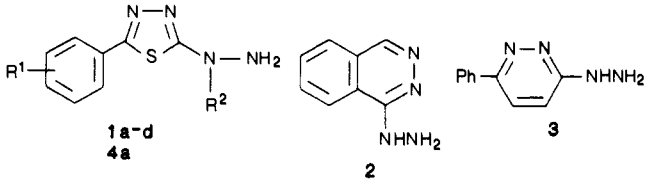
The synthesis and anticonvulsant activity of a series of 2-aryl-5-hydrazino-1,3,4-thiadiazoles are described. The combination of preferred aromatic substituents in the 2-position coupled with alkyl substitution on the hydrazine moiety led to a number of potent compounds lacking sedation, ataxia, or lethality. 5-(2-Biphenylyl)-2-(1-methylhydrazino)-1,3,4-thiadiazole (4m) represents a new class of anticonvulsant agent and compares favorably with the standard drugs phenytoin, phenobarbital, and carbamazepine.

A series of 2-aryl-5-hydrazino-1,3,4-thiadiazoles exemplified by the general structure (1, R^2 = H)[1] were designed as analogues of the known vasodilators hydralazine (2)[2] and the pyridazinylhydrazine 3.[3] Subsequent evaluation of



this series 1 showed that some analogues possessed both antihypertensive activity (vasodilation) and anticonvulsant activity[4] (Table I). Furthermore, it was found that particular substitution in the 2-position of the aromatic ring (i.e., R^1 = 2-Cl, 2-Ph, and 2-hexyloxy) produced compounds with reduced antihypertensive activity but with a desirable anticonvulsant profile.[4] It was also found that methylation on the α-nitrogen (N^1) of the hydrazine group in the *o*-tolyl series (**1a** → **4a**) decreased the vasodilator activity without concurrent decrease in anticonvulsant activity (Table I). Thus a combination of the preferred aromatic substituents in the 2-position coupled with various alkyl and aryl substitution on the hydrazine moiety was a prime objective in this work.

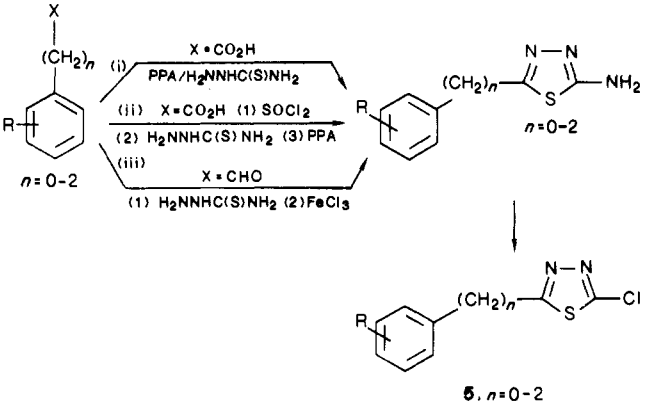
We report here the synthesis and pharmacological evaluation of a series of substituted thiadiazole hydrazines.

Table I

compd	R^1	R^2	DOCA test:[a] % fall in BP at 100 mg/kg, po	ED_{50}, mg/kg, po MMS[b]	ED_{50}, mg/kg, po MES[c]
1a	2-CH_3	H	63	30	>100
1b	2-Cl	H	21	25	70
1c	2-Ph	H	18	33	28
1d	2-$C_6H_{13}O$	H	10	33	20
4a	2-CH_3	CH_3	29	41	75

[a] Screening for antihypertensive activity (maximum percentage fall in mean arterial blood pressure recorded) was carried out with DOCA hypertensive rats (minimum of five) according to the procedures previously reported.[5] [b] MMS = maximum metrazol seizures[6] (mouse). [c] MES = maximum electroshock test[7] (mouse).

Scheme I

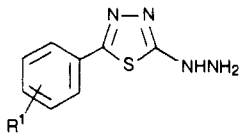


In particular, structure-activity relationships were examined in the 2-CH_3, 2-Cl, 2-Ph and 2-hexyloxy series of compounds (Tables II-VII).

(1) Turner, S. British Patent 1 578 135, 1976.
(2) Druey, J.; Tripod, J. *Medicinal Chemistry*; Schlittler, E., Ed.; Academic: New York, 1967; Vol. 7, Chapter 6.
(3) Druey, J.; Marxer, A. *J. Med. Pharm. Chem.* **1959**, *1*, 1.
(4) Turner, S.; Myers, M. (Reckitt and Colman), unpublished results. See also ref 1.

0022-2623/86/1829-2273$01.50/0

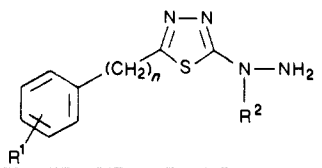
Table II. Unsubstituted Compounds



compd	R^1	method[a]	mp, °C	solvent recrystn	formula	ED_{50},[b] mg/kg (limits) MMS[c]	ED_{50},[b] mg/kg (limits) MES[d]	TD_{50},[b] mg/kg (limits), rotorod[e]
1a[f]	2-CH_3	A	169–172	EtOH	$C_9H_{10}N_4S$·HCl	30 (17–54)	>100	55 (INF)
1b[g]	2-Cl	A	174–176	MeOH	$C_8H_7ClN_4S$·HCl	25 (14–45)	70 (49–99)	>568
1c[h]	2-Ph	A	176–179	EtOH	$C_{14}H_{12}N_4S$·HCl	33 (27–39)	28 (19–39)	627 (154–892)
1d[h]	2-$C_6H_{13}O$	A	163–166	*i*-PrOH	$C_{14}H_{20}N_4OS$·HCl	33 (18–50)	20 (13–29)	>150
1e[f]	4-Ph	A	268–269	MeOH/Et_2O	$C_{14}H_{12}N_4S$·HCl	NT	>200	NT

[a] Preparation methods referred to are as follows: A = hydrazines (R^1NHNHR^2) + chlorothiadiazole **5** where A = unsubstituted, A(1) = monosubstituted, A(2) = disubstituted hydrazines; B = alkylation of N^1 with alkyl halide + base; C = alkylation of N^1 via monoacetylated hydrazine; D = alkylation of N^2 via hydrazone and then reduction; E = alkylation of N^2 via diacetylated hydrazine; F = alkylation of N^2 via formylation and reduction; G = Eschweiler–Clark procedure for trisubstituted hydrazines. [b] INF = infinity, NT = not tested. [c] MMS = maximum metrazol seizures[6] (mouse); 1 h after dosing. [d] MES = maximum electroshock test[7] (mouse); 1 h after dosing. [e] Rotorod (mouse)[13] = rotating rod; 1 h after dosing. Limits obtained from a statistical analysis of the test result (Bliss computer assay[17]). See the Experimental Section for a description of the three methods. [f] Route i (Scheme I) for preparation of **5**. [g] Route ii (Scheme I) for preparation of **5**. [h] Route iii (Scheme I) for preparation of **5**. [i] The N^1-benzyl N^2-acetate compound (from method C) was N^2-methylated in the presence of CH_3I/NaH (i.e., method B, usually for N^1-methylation). Acid hydrolysis gave **10f** (see Experimental Section), which was converted to **13b** by method G. [j] The N^1-benzyl N^2-acetate compound (see footnote *i* above) was reduced directly with borane (analogous to formylation/reduction; method F) to give **10g**.

Table III. N^1-Monosubstituted Compounds



no.	R^1	R^2	*n*	method[a]	mp, °C	solvent recrystn	formula	ED_{50},[b] mg/kg (limits) MMS[c]	ED_{50},[b] mg/kg (limits) MES[d]	TD_{50},[b] mg/kg (limits), rotorod[e]
4a	2-CH_3	CH_3	0	A(1) or A, C	203–204	MeOH	$C_{10}H_{12}N_4S$·HCl	41 (29–57)	75 (55–103)	108 (INF)
4b	2-CH_3	*i*-Pr	0	A, B	224–225	EtOH/Et_2O	$C_{12}H_{16}N_4S$·HCl	49 (INF)	54 (34–91)	NT
4c	2-CH_3	*n*-Bu	0	A, C	170–173	EtOH	$C_{13}H_{18}N_4S$·HCl	60 (41–108)	119 (66–732)	NT
4d	2-CH_3	Ph	0	A(1)	149–150	*i*-PrOH	$C_{15}H_{14}N_4S$	>100	>100	>400
4e	2-CH_3	$PhCH_2$	0	A(1) or A, C	85–87	*n*-hexane	$C_{16}H_{16}N_4S$	44 (1–96)	27 (INF)	>200
4f	2-Cl	CH_3	0	A(1)	205–209	EtOH	$C_9H_9ClN_4S$·HCl	41 (24–64)	20 (INF)	136 (78–253)
4g	2-Cl	*i*-Pr	0	A, B	168–169	EtOH/H_2O	$C_{11}H_{13}ClN_4S$	>100	54 (23–129)	>800
4h	2-Cl	CH_2OCH_3	0	A, B	101–103	Et_2O	$C_{10}H_{11}ClN_4OS$	60 (40–88)	50 (14–179)	80 (INF)
4i	2-Cl	Ph	0	A(1)	213–216	$(Me)_2CO$	$C_{14}H_{11}ClN_4S$	>100	>100	NT
4j	2-Cl	$PhCH_2$	0	A(1)	103–104	EtOAc/petrol	$C_{15}H_{13}ClN_4S$	143 (INF)	186 (123–276)	NT
4k	2-Cl	$Ph(CH_2)_2$	0	A, B	114–116	$CHCl_3$/petrol	$C_{16}H_{15}ClN_4S$	~200	>100	NT
4l	2-Cl	c-C_6H_{11}	0	A, B	244–247	$CHCl_3/Et_2O$	$C_{14}H_{17}ClN_4S$·HCl	>100	>100	NT
4m	2-Ph	CH_3	0	A(1)	164–165	EtOAc/petrol	$C_{15}H_{14}N_4S$	27 (17–46)	18 (13–25)	>1000
4n	2-Ph	*i*-Pr	0	A, B	179–180	EtOAc/petrol	$C_{17}H_{18}N_4S$	>100	>100	NT
4o	2-Ph	Ph	0	A(1)	187–188	EtOH/H_2O	$C_{20}H_{16}N_4S$	>100	>100	NT
4p	2-Ph	$PhCH_2$	0	A, B,	105–110	EtOH/H_2O	$C_{21}H_{18}N_4S$·HCl	>200	>200	NT
4q	2-$C_6H_{13}O$	CH_3	0	A(1)	155–156	EtOH/Et_2O	$C_{15}H_{22}N_4OS$·HCl	27 (17–36)	26 (20–24)	~160
4r	4-Ph	CH_3	0	A(1)	222–223	EtOH/H_2O	$C_{15}H_{14}N_4S$	NT	>200	NT
4s[h]	2-OPh	CH_3	0	A(1)	229–231	EtOH/Et_2O	$C_{15}H_{14}N_4OS$·HCl	33 (INF)	33 (INF)	<400
4t[h]	3-OPh	CH_3	0	A(1)	126–128	EtOH/H_2O	$C_{15}H_{14}N_4OS$	111 (INF)	100 (INF)	NT
4u[h]	2-SPh	CH_3	0	A(1)	193–195	EtOH/Et_2O	$C_{15}H_{14}N_4S_2$·HCl	27 (1–46)	43 (INF)	NT
4v[h]	2-Ch_2Ph	CH_3	0	A(1)	175–179	EtOH/Et_2O	$C_{16}H_{17}ClN_4S$·HCl·H_2O	54 (41–77)	50 (36–70)	NT
4w[f]	H	CH_3	1	A(1)	189–192	EtOH/H_2O	$C_{10}H_{12}N_4S$·HCl	25 (14–40)	11 (3–19)	280 (INF)
4x[f]	H	CH_3	2	A(1)	180–183	EtOH/Et_2O	$C_{11}H_{14}N_4S$·HCl	49 (INF)	51 (34–INF)	317 (260–398)

[a–f,h] Same as for Table II.

Chemistry

Construction of the thiadiazole ring was achieved by using one of the three standard cyclization procedures[8] shown in Scheme I. Diazotization of the amine in the usual way gave the intermediate chloro compound **5**.[9] The hydrazines prepared from **5** are discussed in terms of their substitution pattern and are shown in Scheme II.

(a) Unsubstituted Compounds 1a–e (Table II). Treatment of **5** with hydrazine hydrate gave the unsubstituted hydrazines **1a–e** in high yield (method A).

(5) Stanton, H. C.; White, J. B. *Arch. Int. Pharmacodyn. Ther.* **1966**, *154*, 351. Weeks, J. R.; Jones, J. A. *Proc. Exp. Biol. Med.* **1960**, *104*, 646.

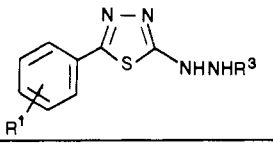
(6) Soaje-Echaque, E.; Lim, R. K. S. *J. Pharmacol. Exp. Ther.* **1962**, *138*, 224. Desmedt, L. K. C.; Niemegeers, C. J. E.; Lewi, P. J.; Janssen, P. A. J. *Arzneim.-Forsch. (Drug Res.)* **1976**, *26*, 1592.

(7) Tulloch, I. F.; Water, D. S.; Howe, G. M.; Howe, S. J. *Neuropharmacology* **1982**, *21*, 555.

(8) For example see: Maffii, G.; Testa, E.; Ettorre, R. *Farmaco, Ed. Sci.* **1958**, *13*, 187.

(9) Kanaoka, M. *Pharm. Bull.* **1957**, *5*, 385. Potts, K. T.; Huseby, R. M. *J. Org. Chem.* **1966**, *31*, 3528.

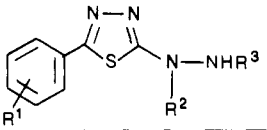
Table IV. N^2-Monosubstituted Compounds



no.	R^1	R^3	method[a]	mp, °C	solvent recrystn	formula	ED_{50},[b] mg/kg (limits) MMS[c]	ED_{50},[b] mg/kg (limits) MES[d]	TD_{50},[b] mg/kg (limits), rotorod[e]
6a	2-CH_3	CH_3	A, E	81–83	Et_2O	$C_{10}H_{12}N_4S$	>100	>100	NT
6b	2-CH_3	*i*-Pr	A, D	135–136	EtOAc/hexane	$C_{12}H_{16}N_4S$	54 (INF)	83 (59–123)	449 (314–INF)
6c	2-CH_3	c-C_5H_9	A, D	147–148	$(Me)_2CO$	$C_{14}H_{18}N_4S$·HCl	>100	>100	NT
6d	2-CH_3	Ph	A(1)	144–147	*i*-PrOH	$C_{15}H_{14}N_4S$	>100	>100	NT
6e	2-CH_3	$CH(Ph)_2$	A, D	162–163	EtOAc/petrol	$C_{22}H_{20}N_4S$	>100	>200	NT
6f	2-Cl	*i*-Pr	A, D	144–145	EtOAc/petrol	$C_{11}H_{13}ClN_4S$	50 (INF)	50 (31–82)	200 (INF)
6g	2-Cl	c-C_5H_9	A, D	149–150	EtOAc/petrol	$C_{13}H_{15}ClN_4S$	>100	>100	NT
6h	2-Cl	Ph	A(1)	172–173	EtOH	$C_{14}H_{11}ClN_4S$	>200	>100	NT
6i	2-Cl	$PhCH_2$	A, D	168–169	$(Me)_2CO$	$C_{15}H_{13}ClN_4S$·HCl	>100	>100	NT
6j	2-Ph	*i*-Pr	A, D	146–147	Et_2O/petrol	$C_{17}H_{18}N_4S$	44 (29–56)	35 (0–52)	NT
6k	2-Ph	Ph	A(1)	171–172	EtOH/H_2O	$C_{20}H_{16}N_4S$·HCl	>100	>100	NT
6l	2-$C_6H_{13}O$	*i*-Pr	A, D	187–188	EtOH/H_2O	$C_{17}H_{26}N_4OS$·HCl	>100	>100	NT
6m	2-$C_6H_{13}O$	c-C_5H_9	A, D	169–171	$(Me)_2CO$	$C_{19}H_{28}N_4OS$·HCl	>100	>100	NT
6n	2-$C_6H_{13}O$	Ph	A(1)	180–181	EtOH/Et_2O	$C_{20}H_{24}N_4OS$·HCl	>100	>100	NT

[a–e] Same as for Table II.

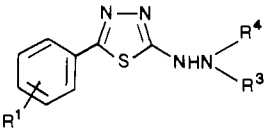
Table V. N^1,N^2-Disubstituted Compounds



no.	R^1	R^2	R^3	method[a]	mp, °C	solvent recrystn	formula	ED_{50},[b] mg/kg (limits) MMS[c]	ED_{50},[b] mg/kg (limits) MES[d]	TD_{50},[b] mg/kg (limits), rotorod[e]
10a	2-CH_3	CH_3	CH_3	A(2)	121–122	Et_2O	$C_{11}H_{14}N_4S$	23 (9–36)	10 (6–15)	72 (52–94)
10b	2-CH_3	CH_3	*i*-Pr	A, D, B	184–185	$(Me)_2CO$	$C_{13}H_{18}N_4S$·HCl	38 (17–51)	35 (INF)	NT
10c	2-CH_3	CH_3	c-C_5H_9	A, D, B	166–167	$(Me)_2CO$/Et_2O	$C_{15}H_{20}N_4S$·HCl	81 (39–108)	110 (85–137)	NT
10d	2-CH_3	CH_3	$CH(Ph)_2$	A(1), D	170–172	EtOAc/petrol	$C_{23}H_{22}N_4S$	>200	>200	NT
10e	2-CH_3	*i*-Pr	CH_3	A, B, F	183–184	EtOH/Et_2O	$C_{13}H_{18}N_4S$·HCl	>100	>100	NT
10f	2-CH_3	$PhCH_2$	CH_3	*i*	183–186	MeOH	$C_{17}H_{18}N_4S$·HCl	93 (INF)	109 (86–167)	341 (243–686)
10g	2-CH_3	$PhCH_2$	CH_3CH_2	A, C, F[j]	174–179	MeOH/Et_2O	$C_{18}H_{20}N_4S$·HCl	>100	>100	NT
10h	2-Cl	CH_3	CH_3	A(2)	113–114	EtOAc/petrol	$C_{10}H_{11}ClN_4S$	25 (INF)	43 (28–62)	106 (INF)
10i	2-Cl	CH_3	*i*-Pr	A, D, B	162–163	$(Me)_2CO$	$C_{12}H_{15}ClN_4S$·HCl	30 (20–54)	16 (11–24)	71 (INF)
10j	2-Cl	CH_3	c-C_5H_9	A, D, B or A(1), D	191–192	EtOH/Et_2O	$C_{14}H_{17}ClN_4S$·HCl	>100	106 (68–286)	NT
10k	2-Cl	CH_3	Ph	A(1), B	140–141	EtOAc/petrol	$C_{15}H_{13}ClN_4S$	>100	>100	NT
10l	2-Cl	*i*-Pr	CH_3	A, B, F	129–130	EtOAc/petrol	$C_{12}H_{15}ClN_4S$	>100	>100	NT
10m	2-Cl	$PhCH_2$	CH_3	A, B, F or A(1), F	143–144	EtOH/Et_2O	$C_{16}H_{15}ClN_4S$·HCl	>100	>100	NT
10n	2-Ph	CH_3	CH_3	A(2)	177–178	EtOH/Et_2O	$C_{16}H_{16}N_4S$·HCl	>100	~100	NT
10o	2-Ph	CH_3	*i*-Pr	A, D, B	174–176	*i*-PrOH	$C_{18}H_{20}N_4S$·HCl	66 (49–86)	55 (38–158)	NT
10p	2-$C_6H_{13}O$	CH_3	CH_3	A(1), F	156–157	$(Me)_2CO$	$C_{16}H_{24}N_4OS$·HCl	39 (31–50)	<250	NT
10q	2-$C_6H_{13}O$	CH_3	*i*-Pr	A, D, B or A(1), D	195–196	EtOH/Et_2O	$C_{18}H_{28}N_4OS$·HCl	56 (20–73)	97 (83–112)	NT

[a–e,i,j] Same as for Table II.

Table VI. N^2-Disubstituted Compounds

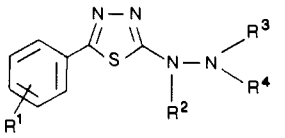


no.	R^1	R^3	R^4	method[a]	mp, °C	solvent recrystn	formula	ED_{50},[b] mg/kg (limits) MMS[c]	ED_{50},[b] mg/kg (limits) MES[d]	TD_{50},[b] mg/kg (limits), rotorod[e]
11a	2-CH_3	CH_3	CH_3	A, D, F	176–179	EtOH/Et_2O	$C_{11}H_{14}N_4S$·HCl	>100	60 (46–73)	>250
11b	2-CH_3	CH_3	*i*-Pr	A, D, F	123–124	EtOH/H_2O	$C_{13}H_{18}N_4S$	>100	140 (96–193)	NT

[a–e] Same as for Table II.

(b) N^1-Monosubstituted Compounds 4a–x (Table III). Direct reaction of **5** with a monoalkylhydrazine (method A(1)) gave predominantly or exclusively the N^1-monosubstituted hydrazine **4**. In contrast phenylhydrazine yielded a mixture of the two possible hydrazines **4** and **6**. The assignment of structure **4** to the alkylhydrazine products was confirmed by the formation of a hydrazone (e.g., with acetone), indicative of a terminal NH_2

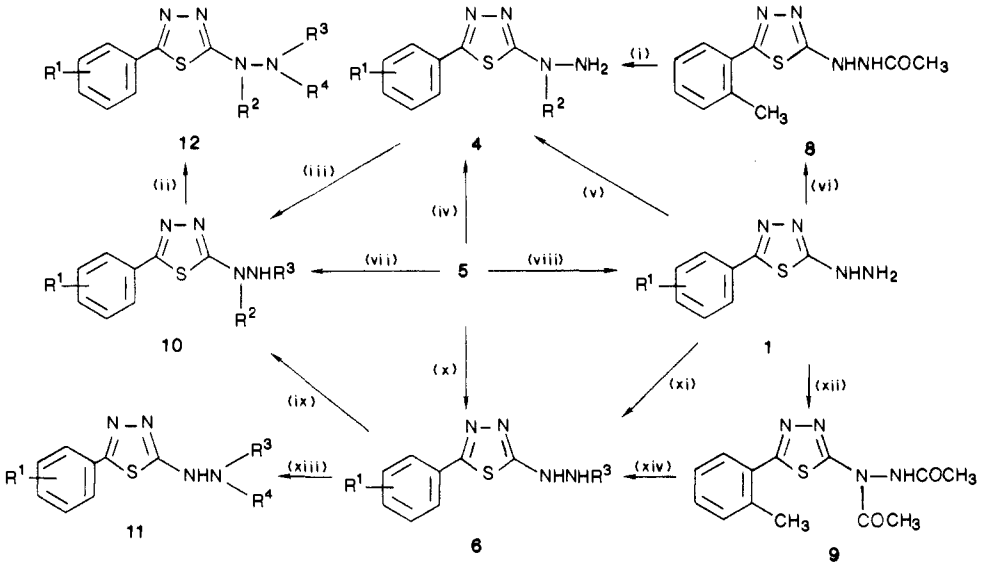
Table VII. Trisubstituted Compounds



no.	R^1	R^2	R^3	R^4	method[a]	mp, °C	solvent recrystn	formula	ED_{50},[b] mg/kg (limits) MMS[c]	ED_{50},[b] mg/kg (limits) MES[d]	TD_{50},[b] mg/kg (limits), rotorod[e]
12a	2-CH_3	CH_3	CH_3	CH_3	A(2), G	77–78	Et_2O	$C_{12}H_{16}N_4S$	68 (46–120)	25 (14–45)	167 (115–228)
12b	2-CH_3	$PhCH_2$	CH_3	CH_3	*i*	140–142	MeOH/Et_2O	$C_{18}H_{20}N_4S$·HCl	>100	>200	NT
12c	2-Cl	CH_3	CH_3	CH_3	A(2), G	142–143	EtOH/Et_2O	$C_{11}H_{13}ClN_4S$·HCl	>100	53 (35–493)	347 (239–779)
12d	2-Cl	*i*-Pr	CH_3	CH_3	A, B, F	113–114	EtOH/Et_2O	$C_{13}H_{17}ClN_4S$·HCl	>200	116 (59–175)	NT
12e	2-Ph	CH_3	CH_3	CH_3	A(2), F	173–174	EtOH/Et_2O	$C_{17}H_{18}N_4S$·HCl	73 (47–123)	63 (INF)	>800

[a–e,i] Same as for Table II.

Scheme II[a]



[a] (i) (a) NaOMe/R^2X, (b) acid. (ii) Method F or HCO_2H/HCHO, method G. (iii) Method D. (iv) R^2NHNH_2, method A(1), R^2 = CH_3, CH_2Ph. (v) Method B, NaH/R^2X. (vi) Method C, Ac_2O/pyr, R^1 = 2-Me. (vii) MeNHNHMe, method A(2), R^2 = R^3 = Me. (viii) NH_2NH_2, method A. (ix) Method B. (x) Method A(1), $PhNHNH_2$ (R^3 = Ph). (xi) Method D, (a) (XY) C=O, (b) BH_3·THF, (c) concentrated HCl. (xii) Ac_2O/pyr, R^1 = 2-Me. (xiii) (a) HCO_2H, (b) BH_3·THF, (c) concentrated HCl; method F. (xiv) Method E. (a) MeI/NaH, (b) aqueous HCl, R^1 = 2-Me, R^3 = Me.

group. In addition, the mass spectrum usually revealed a loss of the terminal NH_2 group.

Other monosubstituted hydrazines **4** (R^2 = $(CH_2)_2Ph$, *i*-Pr, CH_2OCH_3, cyclohexyl) were prepared via alkylation of **1** in the presence of sodium hydride (method B). Confirmation that the alkylation had taken place on N^1 of the hydrazine group was obtained in the example of benzylhydrazine **4j**, which was prepared by the two routes possible, i.e., method A(1) and methods A + B, the products from both procedures being identical. Alkylation of aminothiadiazoles has been observed in earlier reports[10] to give a ring-alkylated product.

(c) N^2-Monosubstituted Compounds 6a–n (Table IV). In initial attempts to synthesize these compounds, an acetyl group was introduced onto N^2 (giving **8**) (method C) with the intention of reversing the relative acidities of the protons located on the two hydrazine nitrogen atoms such that, in the presence of base, proton abstraction and subsequent alkylation would occur to give **6**. However, this was not realized; only the corresponding N^1-substituted compounds **4** were obtained, their structures being confirmed by comparison with authentic samples obtained by method A(1). Diacetylation of **1a** to give **9**, followed by alkylation and acid hydrolysis, finally produced the desired terminal methylated compound **6a** in moderate yield (method E). Utilization of hydrazone formation on the terminal NH_2 group of the hydrazines provided a more efficient route to other N^2-monosubstituted derivatives. It was found that the intermediate hydrazones were readily reduced in high yield with borane or sodium borohydride (method D).

(d) N^1,N^2-Disubstituted Compounds 10a–g (Table V). The simplest hydrazines in this series (**10**, R^2 = R^3 = CH_3) were readily obtained from the reaction of **5** with dimethylhydrazine (method A(2)). Other N^1,N^2-disubstituted hydrazines were prepared by one of two routes using a combination of methods already described.

(e) N^2-Disubstituted Compounds 11a,b (Table VI). Only two compounds were prepared in this series involving an overall methylation of the N^2-monosubstituted hydrazine **6**. This was achieved via N-formylation of **6** followed by reduction with borane[11] to give the corresponding disubstituted product **11** (method F).

(f) Trisubstituted Compounds 12a–e (Table VII). Conversion of N^1,N^2-disubstituted **10** to trisubstituted hydrazines **12** was achieved in two ways utilizing reductive

(10) Katritzky, A. R.; Boulton, A. J. *Adv. Heterocycl. Chem.* **1968**, *9*, 181.

(11) Adembri, G.; Camparini, F.; Ponticelli, F.; Tedeschi, P. *J. Chem. Soc.* **1977**, 971.

Table VIII. Effect of 4m on Maximal Electroshock Seizures[7] (MES) in the Rat and Mouse Compared with Standards

	inhibition of hind limb tonus				
	rat ED_{50}, mg/kg			mouse ED_{50}, mg/kg	
compound	t = 1 h (po)	t = 4 h (po)	at time of peak effect (ip)	t = 1 h (po)	at time of peak effect (ip)
4m	16 (10–21)	11 (3–19)	6 (3–12)	18 (13–25)	17 (12–26)
phenytoin	14 (6–23)	26 (17–39)	14 (10–19)	8 (4–12)	8 (4–9)
phenobarbital	9 (7–13)	3 (2–5)	3 (2–6)	12 (9–15)	18 (13–37)
carbamazepine	4 (2–7)	7 (4–11)	2 (1–3)	20 (17–23)	6 (4–8)

methylations, these being the formylation–diborane reduction procedure (method F) or the Eschweiler–Clark procedure[12] using a formic acid–formaldehyde mixture (method G).

Results and Discussion

The compounds synthesized together with pharmacological evaluation results in three test areas are summarized in Tables II–VII. The metrazol[6] and electroshock[7] tests are an assessment of the anticonvulsant activity while the rotorod test[13] was used to assess the neurotoxicity of the compounds. Only the most interesting derivatives were examined in this latter test situation.

(a) Unsubstituted Compounds (Table II). It had previously been observed[4] that certain specific substituents in the 2-position of the aromatic ring produced compounds (i.e., **1b–d**) that possessed a desirable anticonvulsant profile with considerably reduced neurotoxicity (rotorod results) in comparison to the 2-CH_3 compound **1a**. Interestingly, replacement of the 2-phenyl group (**1c**) by a 4-phenyl (**1e**) caused a complete loss of activity.

(b) N^1-Monosubstituted Compounds (Table III). Methylation of N^1 in **1a** was shown[4] to produce compound **4a**, which retained anticonvulsant activity. Generally it was found that increasing the size of the substituent at N^1 in the 2-chloro and 2-phenyl series resulted in a decrease or loss of activity (i.e., CH_3, *i*-Pr, *n*-Bu, Ph, CH_2Ph, CH_2CH_2Ph, cyclohexyl). One exception to this rule was the benzyl derivative **4e**, which possessed a good profile of activity. The scheme proposed by Topliss[14] for further analogue synthesis suggested that the ether grouping, CH_2OCH_3, in place of CH_3 would enhance the activity. The one compound made, **4h** (cf. **4f**), possessed slightly decreased activity, but was found to be very sedative.

The methylhydrazines proved to be the most potent compounds in this series, especially the benzyl (**4w**), 2-phenyl (**4m**), and 2-hexyloxy (**4q**) derivatives, although the latter produced sedation as observed in the rotorod screen.

(c) N^2-Monosubstituted Compounds (Table IV). Three of the four isopropyl derivatives, **6b**, **6f**, and **6j**, possessed a good level of anticonvulsant activity; the corresponding 2-hexyloxy compound **6l** was inactive. Surprisingly, the methyl derivative **6a** in the 2-CH_3 series retained some of the antihypertensive activity inherent in the parent hydrazine **1a** (see Table I) and was lacking anticonvulsant activity. The Topliss[14] scheme suggested that better activity could be expected if the isopropyl group was replaced by cyclopentyl or benzyl groups. However, activity was lost in the subsequent compounds that were synthesized (compare **6b** with **6c** and **6f** with **6g** and **6i**).

(d) N^1,N^2-Disubstituted Compounds (Table V). Disubstitution with lower alkyl groups in the 2-CH_3 and 2-Cl series produced potent anticonvulsant compounds, but this activity was associated with an increased and unacceptable level of neurotoxicity (i.e., **10a**, **10h**, and **10i**). The separation of the two actions in these two series was never achieved. However, although the potency was somewhat reduced, sedation was not apparent in the corresponding derivatives in the 2-phenyl and 2-hexyloxy series (i.e., **10o–q**) (sedation was not observed during the metrazol and electroshock tests; in contrast, sedation (see neurotoxicity in the Experiment Section) was seen with **10a**, **10h**, and **10i** in these test situations). The position of the isopropyl group was critical, activity only being retained when it was attached to N^2 (**10b**, **10i**, **10o**, **10q** active; **10e**, **10l** inactive). When the isopropyl group was replaced by the more lipophilic cyclopentyl group (i.e., **10c** and **10j**), then a considerable reduction in activity was observed.

Table IX. Effect of **4m** on Maximal Metrazol Seizures[6] (MMS) in the Rat and Mouse Compared with Standards

	inhibition of hind limb tonus			
	rat ED_{50}, mg/kg		mouse ED_{50}, mg/kg	
compound	t = 1 h (po)	t = 4 h (po)	t = 1 h (po)	at time of peak effect (ip)
4m	13 (4–19)	13 (9–18)	27 (17–46)	21 (13–30)
phenytoin	12 (9–16)	20 (11–31)	8 (6–11)	12 (5–24)
phenobarbital	4 (2–5)	5 (3–8)	4 (3–6)	6 (3–8)
carbamazepine	3 (2–5)	5 (3–7)	11 (2–16)	16 (11–23)

(e) N^2-Disubstitution (Table VI). Disubstitution on the terminal nitrogen atom was not extensively studied. A reduction in activity was seen with the two compounds prepared in the 2-CH_3 series in comparison to the unsubstituted hydrazine **1a**.

(f) Trisubstitution (Table VII). The trimethylated derivatives **12a**, **12c**, and **12e** all retained activity albeit at a lower level than the corresponding parent hydrazines **1a–c**. Substitution of the methyl group on N^1 by larger groups considerably reduced this activity as seen with **12b** and **12d**.

Of all the hydrazines examined, the most promising profile of activity is found in compounds based on the 2-Ph series. Compounds based on the 2-hexyloxy series generally showed similar potency but, with the exception of **10q**, appeared to be more sedative. The 2-phenyl substituent is a bulky lipophilic group, and this may be contributing to the improved profile shown by this subseries (cf. the 2-CH_3 and 2-Cl series); yet lipophilicity is not the overriding consideration as demonstrated by the sedative side effects observed with the 2-hexyloxy series and the inactivity of the 4-phenyl compound **1e**.

At the inception of this program, the need was recognized for an orally-active compound with potent activity against grand mal and partial epilepsy, with a medium duration of activity, and, most importantly, with fewer adverse side effects than currently prescribed drugs. The *N*-methylhydrazine in the 2-Ph series (**4m**) was considered to have the most primising overall profile from the primary pharmacological program and was therefore investigated further and compared with some established anticonvulsant agents. Table VIII shows the ED_{50} values in the

(12) Adams, R. *Organic Reactions*; Wiley: New York, 1949; Vol. 5, Chapter 7, p 307.
(13) Collier, H. O. J.; Fieller, E. C.; Hall, R. A. *Analyst (London)* **1949**, *74*, 592.
(14) Topliss, J. G. *J. Med. Chem.* **1972**, *15*, 1006.

Table X. Effect of 4m and Standards on Mouse Motor Performance in the Rotorod Test[13] and Protective Indices, Based on Plasma Concentrations, in the Rat[15]

compound	TD_{50},[a] mg/kg (mouse) at 1 h (po)	TD_{50},[a] mg/kg (mouse) at time of peak effect (ip)	protective index[15] (rat)
4m	>1000 (800 at 2 h)	93 (63–125)	5.14
phenytoin	216 (154–319)	56 (27–74)	5.17
phenobarbital	68 (52–92)	86 (54–146)	2.42
carbamazepine	166 (104–282)	67 (29–108)	2.51

[a] Dose at which 50% of trained animals fall off the rotorod.

maximum electroshock (MES) test[7] for **4m** and some standard compounds after oral dosage and at the time of peak effect after intraperitoneal dosage. Similarly Table IX shows the corresponding ED_{50} values in the maximum metrazol seizure (MMS) test.[6] The results show that in both rodent models the potency of **4m** falls within the same range as those of the standards. In the mouse, motor impairment, as judged by the rotorod test,[13] was very slight at high oral doses whereas a relatively low TD_{50} value was obtained following intraperitoneal dosage (Table X). This disparity is probably due to limited absorbtion after po administration. On a dosage basis, however, **4m** is slightly less neurotoxic than phenytoin and carbamazepine and shows a similar neurotoxic TD_{50} value to that of phenobarbital in this test. The protective indices of some anticonvulsant drugs have recently been measured[15] by dividing the plasma concentrations at which side effects occur by the plasma concentration at which anticonvulsant activity occurs rather than by comparison of doses. This approach has been adopted for determining the protective index of **4m** in the rat where plasma concentrations were 57 μg/mL (rotorod test) and 11.1 μg/mL (MES test), giving a protective index of 5.14[16] (Table X). It can be seen that **4m** has a protective index comparable with that of phenytoin and twice that of phenobarbital and carbamazepine. In addition, at anticonvulsant doses it can be demonstrated that **4m** has no effect on either heart rate or blood pressure.[16]

In summary, *N*-methylhydrazine **4m** in rodent models of grand mal epilepsy has anticonvulsant activity, the potency of which is comparable with that of established drugs. No neurotoxicity or cardiovascular actions of **4m** occur at anticonvulsant doses, showing a good separation between the beneficial effects and side effects of this compound.

Experimental Section

Chemistry. All melting points were determined on a Kofler hot stage apparatus or a Büchi apparatus in glass capillary tubes and are uncorrected. IR, NMR, and mass spectra were recorded for all compounds on Perkin-Elmer 700 and 710B and Varian Associates T-60 and LKB-2091 instruments and were consistent with the assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values. Where purifications were carried out by column chromatography, silica refers to Kieselgel 60 (70–235 mesh).

The chlorothiadiazoles **5** were prepared following routine literature procedures.[8,9]

Yields are given for all hydrazines prepared by methods A, A(1), and A(2). These compounds were also used to prepare all the substituted hydrazines shown in Tables II–VII; yields of representative examples are given for the other preparative methods.

Method A. 2-Hydrazino-5-(2-methylphenyl)-1,3,4-thiadiazole Hydrochloride (1a). A mixture of 2-chloro-5-(2-methylphenyl)-1,3,4-thiadiazole (**5**) (3.0 g, 14.2 mmol) and hydrazine hydrate (4.28 g, 85.5 mmol) in EtOH (80 mL) was heated under reflux for 2 h. After removal of solvent, water was added and the mixture filtered. The residue was dissolved in hot 2 N HCl (20 mL) and cooled, and the precipitate was filtered off and crystallized from ethanol to give **1a**: yield 1.62 g (47%); mp 169–172 °C. Anal. ($C_9H_{10}N_4S$·HCl) C, H, N.

The following compounds were also prepared by method described above: **1b** (45%), **1c** (29%), **1d** (34%), **1e** (13%).

Method A(1). 5-(2-Biphenylyl)-2-(1-methylhydrazino)-1,3,4-thiadiazole (4m). To a solution of **5** (60 g, 220 mmol) in EtOH (3000 mL) was added methylhydrazine (38.4 g, 834 mmol), and the mixture was stirred for 2.5 h at 85 °C. After removal of solvent, the residue was partitioned between water and CH_2Cl_2. The organic layer was collected, washed with water, dried, and evaporated to leave 52.4 g of a yellow solid. Recrystallization from EtOAc/petroleum ether (bp 60–80 °C) gave **4m**: yield 34.3 g (55%); mp 164–165 °C. Anal. ($C_{15}H_{14}N_4S$) C, H, N.

The reactions with phenylhydrazine were conducted in *n*-BuOH as the solvent under 24-h reflux conditions. The solvent was removed in vacuo and the residue partitioned between Et_2O and water. Any undissolved solid was collected and recrystallized to give the N^1-substituted compound. The ethereal extracts were collected, washed with water, dried, and evaporated to leave the N^2-substituted compound. Alternatively, the two phenylhydrazine products could be separated chromatographically, using silica and eluting with Et_2O/*n*-hexane.

The following compounds were prepared by using the above procedure: **4a** (51%), **4d** (13%), **4e** (39%), **4f** (56%), **4i** (21%), **4j** (49%), **4o** (22%), **4p** (29%), **4q** (51%), **4r** (26%), **4s** (47%), **4t** (16%), **4u** (48%), **4v** (40%), **4w** (91%), **4x** (21%), **6d** (7%), **6h** (4%), **6k** (15%), and **6n** (4%).

Method A(2). 5-(2-Biphenylyl)-2-(1,2-dimethylhydrazino)-1,3,4-thiadiazole Hydrochloride (10n). To a solution of 1,2-dimethylhydrazine dihydrochloride (11.12 g, 83.6 mmol) in EtOH (80 mL) was added NaOMe (8.54 g, 158 mmol). After the mixture was stirred for 1 h at room temperature, a solution of **5** (6 g, 22 mmol) in ethanol (30 mL) was added and the mixture was heated under reflux for 24 h. Solvent was removed in vacuo and the residue partitioned between $CHCl_3$ and water. The organic layer was washed with water, dried, and evaporated to leave an oil, which was chromatographed on silica, eluting with $CHCl_3$ initially followed by $CHCl_3$/MeOH (1:50–1:5 mixtures), to give 3.2 g of an oil. This oil was dissolved in Et_2O and treated with ethereal HCl. The solid (3.3 g) was collected and recrystallized from EtOH/Et_2O to give **10n**: yield 1.76 (24%); mp 177–178 °C. Anal. ($C_{16}H_{16}N_4S$·HCl) C, H, N.

Compounds **10a** (78%) and **10h** (36%) were also prepared by using the above procedure.

Method B. 5-(2-Chlorophenyl)-2-(1-phenethylhydrazino)-1,3,4-thiadiazole (4k). To a stirred mixture of NaH (0.48 g of a 50% dispersion in oil, 10 mmol) and DMF (20 mL) was added a solution of 5-(2-chlorophenyl)-2-hydrazino-1,3,4-thiadiazole (**1b**) (2.26 g, 10 mmol) in DMF (10 mL). After a further 0.5 h a solution of phenethyl bromide (1.85 g, 10 mmol) in DMF (10 mL) was added dropwise. The reaction was carried out under an atmosphere of nitrogen. After 18 h water was added and the mixture was extracted with $CHCl_3$. The combined extracts were washed with water, dried, and evaporated to leave a brown oil. Purification by chromatography on silica eluting with $CHCl_3$ gave 0.8 g of a solid, which was recrystallized from $CHCl_3$/petroleum ether (bp 60–80 °C) to give **4k**: yield 0.5 g (15%); mp 114–116 °C. Anal. ($C_{16}H_{15}ClN_4S$) C, H, N.

The above procedure was also used in the preparation of **4b**, **4g**, **4h**, **4l**, **4n**, **4p**, **10b**, **10c**, **10i–m**, **10o**, **10g**, and **12d**.

Method C. 2-(1-Benzylhydrazino)-5-(2-methylphenyl)-1,3,4-thiadiazole (4e). To a stirred solution of **1a** (30 g, 123 mmol) in anhydrous pyridine (120 mL) was added dropwise Ac_2O (12.72 g, 125 mmol) over a period of 0.75 h while the temperature was maintained below 10 °C. After a further 3 h at room temperature the solvent was removed in vacuo and water was added to the residual oil, which then solidified. The solid was collected, washed with water, and recrystallized from EtOAc to give 2-(2-acetylhydrazino)-5-(2-methylphenyl)-1,3,4-thiadiazole (**8**): yield 8.2 g

(15) Masuda, Y.; Ursai, Y.; Shiraishi, Y.; Karasawa, T.; Yoshida, K.; Shimuzu, M. *Epilepsia* **1979**, *20*, 623.
(16) Walter, D. S.; Tulloch, I. F.; Flockhart, I. R., unpublished results.

(27%); mp 173–175 °C; MS, 248 (M^+) ($C_{11}H_{12}N_4OS$ requires M^+ 248). To a solution of **8** (8.2 g, 33 mmol) and NaOMe (1.8 g, 33 mmol) in MeOH (40 mL) was added with stirring a solution of benzyl bromide (5.8 g, 34 mmol) in MeOH (35 mL). The reaction was conducted under an atmosphere of nitrogen. After 18 h at room temperature the solvent was removed in vacuo and the residue partitioned between Et_2O and water. The organic extracts were washed with water, dried, and evaporated to leave a solid (10.7 g), which was purified by chromatography on silica. Elution with Et_2O gave the intermediate 2-(2-acetyl-1-benzylhydrazino)-5-(2-methylphenyl)-1,3,4-thiadiazole (7.8 g). A mixture of this intermediate and 50% aqueous HCl was heated under reflux for 6 h. Neutralization with aqueous NH_3 followed by extraction with Et_2O led to the isolation of an impure solid (6 g). Crystallization from *n*-hexane gave **4e**: yield 3.8 g (39% from **8**); mp 85–87 °C. Anal. ($C_{16}H_{16}N_4S$) C, H, N.

Compounds **4a**, **4c**, and **10g** were also prepared by using the above procedure. In addition, the intermediate 2-acetyl-1-benzylhydrazine compound was methylated in the presence of MeI and NaH by using the procedure described in method B. This was followed by hydrolysis with 50% aqueous HCl as described above to give the 1-benzyl-2-methyl derivative **10f**.

Method D. 5-(2-Biphenylyl)-2-(2-isopropyl-1-methylhydrazino)-1,3,4-thiadiazole Hydrochloride (10o). A solution of **4m** (10.5 g, 37 mmol) in $(Me)_2CO$ (100 mL) and five drops of ethereal HCl was heated under reflux for 1 h. The solution was then evaporated to dryness to leave the crude hydrazone intermediate (11.6 g), which was then dissolved in EtOH (50 mL) and treated with $NaBH_4$ (6 g, 159 mmol) at 0 °C. After a further 16 h at room temperature, solvent was removed in vacuo and the residue was heated on a steam bath with water for 0.5 h and then treated with a saturated aqueous solution of sodium potassium tartrate (120 mL). The product was extracted with EtOAc, and the combined extracts were dried and evaporated to leave the impure hydrazine (8.5 g). This solid was dissolved in EtOH and treated with ethereal HCl followed by removal of solvent in vacuo. The residual solid was recrystallized from *i*-PrOH to give **10o**: yield 5.1 g (38%); mp 174–176 °C. Anal. ($C_{18}H_{20}N_4S$·HCl) C, H, N.

Reduction of the hydrazone could also be carried out with use of a 1 M solution of borane in tetrahydrofuran at 0 °C (see method F). The methods described above were used to prepare compounds **6b**, **6c**, **6e–g**, **6i**, **6j**, **6l**, **6m**, **10b–d**, **10i**, **10j**, **10g**, **11a** and **11b**.

Method E. 2-(2-Methylhydrazino)-5-(2-methylphenyl)-1,3,4-thiadiazole (6a). To a cooled, stirred solution of **1a** (3.1 g, 12.8 mmol) in anhydrous pyridine (12 mL) was added dropwise over 1 h Ac_2O (2.6 g, 25.5 mmol). After 3 days at room temperature, solvent was removed to leave a residue, which solidified on stirring with water. The collected solid (3.2 g) was crystallized from EtOAc to give 2-(1,2-diacetylhydrazino)-5-(2-methylphenyl)-1,3,4-thiadiazole (**9**): yield 0.8 g (22%); mp 113–125 °C; MS, 290 (M^+) ($C_{13}H_{14}N_4O_2S$ requires M^+ 290). (It was subsequently found that crystallization, which only gives poor recovery of compound, is not necessary and the crude product can be used directly.)

A mixture of **9** (13.5 g, 47 mmol), NaH (3.9 g of a 50% dispersion in oil, 81 mmol), and anhydrous DMF (70 mL) was stirred at room temperature for 0.5 h. A solution of MeI (12.4 g, 87 mmol) in anhydrous DMF (60 mL) was added and the mixture stirred for a further 24 h. Evaporation of the solvent gave an oily residue, which was partitioned between Et_2O/C_6H_6 and water. The extracts were dried and evaporated to leave a solid (12.6 g), which was triturated with Et_2O to give 2-(1,2-diacetyl-2-methylhydrazino)-5-(2-methylphenyl)-1,3,4-thiadiazole: yield 6.89 g (49% from **9**); mp 131–134 °C; IR max (Nujol) 1690 cm^{-1}. This solid was added to 50% aqueous HCl solution and the mixture heated under reflux for 0.5 h. Basification with aqueous $NaHCO_3$ solution followed by extraction with Et_2O gave a solid (4.9 g), which on trituration with Et_2O (20 mL) gave **6a**: yield 2.6 g (25% from **9**); mp 81–83 °C. Anal. ($C_{10}H_{12}N_4S$) C, H, N.

Method F. 5-(2-Biphenylyl)-2-(1,2,2-trimethylhydrazino)-1,3,4-thiadiazole Hydrochloride (12e). A mixture of **10n** (2 g, 6 mmol) and formic acid (8.4 mL, 250 mmol) was stirred and heated at 85 °C for 2 h. The mixture was poured into water and Et_2O, and the organic extracts were washed with water, dried, and evaporated to leave the impure 5-(2-biphenylyl)-2-(1,2-dimethyl-2-formylhydrazino)-1,3,4-thiadiazole: yield 2.1 g. A solution of the formyl compound in anhydrous THF (80 mL) was cautiously added to a 1 M solution of borane in THF (70 mL) at 0 °C. The solution was allowed to stand at room temperature for 16 h. EtOH (70 mL) was added cautiously to destroy excess reducing agent, and then the solution was evaporated to leave an oily residue. The residue was stirred with a mixture of $CHCl_3$ (200 mL) and concentrated HCl (20 mL) for 16 h. Water (50 mL) was added followed by basification with concentrated NH_3. The product was extracted with $CHCl_3$, and the combined extracts were washed with water, dried, and evaporated to leave an oil, which solidified on standing. The solid was dissolved in EtOH and treated with ethereal HCl followed by Et_2O. The precipitated hydrochloride salt was collected (2 g) and recrystallized from $EtOH/Et_2O$ to give **12e**: yield 0.93 g (45%); mp 173–174 °C. Anal. ($C_{17}H_{18}N_4S$·HCl) C, H, N. Compounds **10e**, **10l**, **10m**, **10p**, **11a**, **11b**, and **12d–e** were also prepared by using this procedure.

2-(1-Benzyl-2-ethylhydrazino)-5-(2-methylphenyl)-1,3,4-thiadiazole Hydrochloride (10g). The intermediate 2-(2-acetyl-1-benzylhydrazino)-5-(2-methylphenyl)-1,3,4-thiadiazole (4.8 g, 14 mmol) described above in method C was used to prepare the crude product as its free base (5.1 g). The hydrochloride salt was prepared in the usual way and recrystallized from $MeOH/Et_2O$ to give **10g**: yield 3.2 g (63%); mp 174–179 °C. Anal. ($C_{18}H_{20}N_4S$·HCl) C, H, N.

Method G. 5-(2-Chlorophenyl)-2-(1,2,2-trimethylhydrazino)-1,3,4-thiadiazole Hydrochloride (12c). A mixture of **10h** (2 g, 8 mmol), formaldehyde (2 mL), and 98% formic acid (2 mL) was heated at 100 °C with stirring for 24 h. The mixture was allowed to cool and then partitioned between water and Et_2O. Extraction with Et_2O followed by washing of the extracts with water, drying, and evaporation gave an oil. This oil was chromatographed on silica, eluting with $CHCl_3$, to give the impure product, which was converted to its hydrochloride salt (1.2 g). Recrystallization from $EtOH/Et_2O$ gave **12c**: yield 0.91 g (38%); mp 142–143 °C. Anal. ($C_{11}H_{13}ClN_4S$·HCl) C, H, N.

Compound **12a** was prepared by using the above procedure.

Pharmacology. General Methods. Male Sprague–Dawley rats in the weight range 90–110 g were used in the maximal electroshock seizures (MES) and neurotoxicity tests; female rats were used in the maximal metrazol seizure (MMS) test. Male mice (BKW, LACA origin) in the weight range 18–22 g were used in the mouse anticonvulsant and rotorod tests. Compounds were dissolved or suspended in a 2% mixture of Tween 80 in distilled water and injected intraperitoneally (ip) or per os (po). The vehicle was inactive in all the test procedures.

Maximal Electroshock Seizure Test. Maximal seizures were induced by application of an electric current across the brain via corneal electrodes.[7] The stimulus parameters for rats were 4-ms pulses of 50 Hz and 150 V for 0.35 s, and for mice were 4-ms pulses of 50 Hz and 80 V for 0.3 s (SRI Ltd., Square stimulator 6052 apparatus). The dose at which the hind limb tonic seizure was blocked in 50% of the animals (ED_{50} value) was determined by probit analysis: the computerized method of Bliss, described by Finney,[17] was used.

Maximal Metrazol Seizure Test. The method for the rat followed closely that of Desmedt et al.[6] Metrazol (leptazol; 80 mg kg^{-1}) was injected intravenously 1 h after oral dosage of the anticonvulsant drug. For the mouse metrazol test, 120 mg/kg was injected intraperitoneally 1 h after oral dosage of the anticonvulsant drug. The ED_{50} value (hind limb tonic seizure) was determined in the same manner as that described in the MES test.

Rotorod Test. Separate groups of rats and mice were trained to stay on a rotorod that rotated at 16 rpm. The drum diameter for rats was 10 cm and for mice was 3 cm. With trained animals, the ability to stay on the rod for the required duration was retained for up to 48 h.[7] Trained animals were dosed with the test compound or the standard drugs or drug vehicle and were tested at timed intervals to measure the effects of the drug on motor performance. The dose at which 50% of the animals fell off the

(17) Finney, D. J. *Probit Analysis*; Cambridge University Press: New York, 1962.

rotorod (TD_{50} value) was determined by probit analysis.

Neurotoxicity. In addition to scoring neurotoxicity by the rotorod test, visual observation of sedation, ataxia, loss of righting reflex, and death after oral dosage of the anticonvulsant drugs were performed and noted prior to testing for anticonvulsant activity.

Measurement of Plasma Concentration. Compound 4m was suspended in 2% Tween 80 in distilled water and injected at a dose volume of 0.5 mL/100 g to groups of six rats either ip or po. At various times after dosing, 1 mL of blood was removed from the rat by cardiac puncture into a lightly heparinized syringe and placed in a heparinized tube. Plasma was prepared by centrifugation, from which 4m was extracted and measured by HPLC with UV detection[16] on a Spherisorb 5-μm ODS column, mobile phase 1% acetic acid/methanol/0.1% aqueous ammonium acetate, 45:55 by volume.

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Registry No. **1a**, 59758-33-7; **1a**·HCl, 65871-41-2; **1b**, 59758-29-1; **1b**·HCl, 65871-45-6; **1c**, 104070-56-6; **1c**·HCl, 104071-21-8; **1d**, 104070-57-7; **1d**·HCl, 104071-22-9; **1e**, 104070-58-8; **1e**·HCl, 104071-23-0; **4a**, 104070-59-9; **4a**·HCl, 65871-74-1; **4b**, 104070-60-2; **4b**·HCl, 104071-24-1; **4c**, 104070-61-3; **4c**·HCl, 104071-25-2; **4d**, 104070-62-4; **4e**, 104070-63-5; **4f**, 104070-64-6; **4f**·HCl, 104071-26-3; **4g**, 104070-65-7; **4h**, 104070-66-8; **4i**, 104070-67-9; **4j**, 104070-68-0; **4k**, 104070-69-1; **4l**, 104070-70-4; **4l**·HCl, 104071-27-4; **4m**, 104070-71-5; **4n**, 104070-72-6; **4o**, 104070-73-7; **4p**, 104070-74-8; **4p**·HCl, 104071-28-5; **4q**, 104070-75-9; **4q**·HCl, 104071-29-6; **4r**, 104070-76-0; **4s**, 104070-77-1; **4s**·HCl, 104071-30-9; **4t**, 104070-78-2; **4u**, 104070-79-3; **4u**·HCl, 104071-31-0; **4v**, 104070-80-6; **4v**·2HCl, 104071-32-1; **4w**, 104070-81-7; **4w**·HCl, 104071-33-2; **4x**, 104070-82-8; **4x**·HCl, 104071-34-3; **5a**, 40642-55-5; **5b**, 36894-93-6; **5c**, 104071-58-1; **5d**, 104071-59-2; **5e**, 91660-26-3; **5s**, 104071-60-5; **5t**, 104071-61-6; **5u**, 104071-62-7; **5v**, 104071-63-8; **5w**, 40288-17-3; **5x**, 104071-64-9; **6a**, 104070-83-9; **6b**, 104070-84-0; **6c**, 104070-85-1; **6c**·HCl, 104071-35-4; **6d**, 104070-86-2; **6e**, 104070-87-3; **6f**, 104070-88-4; **6g**, 104070-89-5; **6h**, 104070-90-8; **6l**, 104070-91-9; **6i**·HCl, 104071-36-5; **6j**, 104070-92-0; **6k**, 104070-93-1; **6k**·HCl, 104071-37-6; **6l**, 104070-94-2; **6l**·HCl, 104071-38-7; **6m**, 104070-95-3; **6m**·HCl, 104071-39-8; **6n**, 104070-96-4; **6n**·HCl, 104071-40-1; **8**, 65871-42-3; **9**, 104071-67-2; **10** (R^1 = 2-Me, R^2 = $PhCH_2$, R^3 = Ac), 104071-70-7; **10a**, 104070-97-5; **10b**, 104070-98-6; **10b**·HCl, 104071-41-2; **10c**, 104070-99-7; **10c**·HCl, 104071-42-3; **10d**, 104071-00-3; **10e**, 104071-01-4; **10e**·HCl, 104071-43-4; **10f**, 104071-02-5; **10f**·HCl, 104071-44-5; **10g**, 104071-03-6; **10g**·HCl, 104071-45-6; **10h**, 104071-04-7; **10i**, 104071-05-8; **10i**·HCl, 104071-46-7; **10j**, 104071-06-9; **10j**·HCl, 104071-47-8; **10k**, 104071-07-0; **10l**, 104071-08-1; **10m**, 104071-09-2; **10m**·HCl, 104071-48-9; **10n**, 104071-10-5; **10n**·HCl, 104071-49-0; **10o**, 104071-11-6; **10o**·HCl, 104071-50-3; **10p**, 104071-12-7; **10p**·HCl, 104071-51-4; **10q**, 104071-13-8; **10q**·HCl, 104071-52-5; **11** (R^1 = 2-Me, R^3 = $PhCH_2$, R^4 = Ac), 104071-65-0; **11a**, 104071-14-9; **11a**·HCl, 104071-53-6; **11b**, 104071-15-0; **12** (R^1 = 2-Me; R^2 = R^4 = Ac; R^3 = Me), 104071-68-3; **12** (R^1 = 2-Ph; R^2 = R^3 = Me; R^4 = CHO), 104071-69-4; **12a**, 104071-16-1; **12b**, 104071-17-2; **12b**·HCl, 104071-54-7; **12c**, 104071-18-3; **12c**·HCl, 104071-55-8; **12d**, 104071-19-4; **12d**·HCl, 104071-56-9; **12e**, 104071-20-7; **12e**·HCl, 104071-57-0; NH_2NH_2, 302-01-2; $MeNHNH_2$, 60-34-4; $PhNHNH_2$, 100-63-0; $PhCH_2NHNH_2$, 555-96-4; MeNHNHMe, 540-73-8; $PhCH_2CH_2Br$, 103-63-9; Me_2CHBr, 75-26-3; $PhCH_2Br$, 100-39-0; $MeOCH_2Cl$, 107-30-2; PhBr, 108-86-1; cyclopentyl bromide, 137-43-9; 5-(2-biphenylyl)-2-(1-methyl-2-isopropylidenehydrazino)-1,3,5-thiadiazole, 104071-66-1; cyclohexyl bromide, 108-85-0.

Substituted 1,3,4-Thiadiazoles with Anticonvulsant Activity. 2. Aminoalkyl Derivatives

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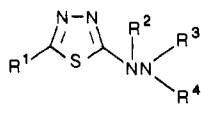
This paper describes the synthesis and pharmacological evaluation of a number of substituted 1,3,4-thiadiazoles. The first member of the series, 2-(aminomethyl)-5-(2-biphenylyl)-1,3,4-thiadiazole (**7**) was found to possess potent anticonvulsant properties in rats and mice and compared favorably with the standard anticonvulsant drugs phenytoin, phenobarbital, and carbamazepine in a number of test situations. The potency of compound **7** was maintained on alkylation of the side-chain nitrogen atom; however, aryl substitution or chain lengthening caused a drop in potency. Replacement of the 2-biphenylyl group by phenyl or benzyl also lead to inactive compounds.

The previous paper[1] has described the anticonvulsant properties of a number of substituted 2-hydrazino-1,3,4-thiadiazoles (**1**). Despite the encouraging pharmacological profiles of many of these compounds, it was recognized that the presence of the hydrazine group in the molecules was potentially undesirable, particularly with respect to the sometimes serious side effects associated with the structurally related compound hydralazine.[2] Consequently a number of the corresponding aminoalkyl derivatives (**2**)



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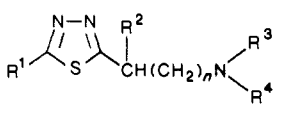
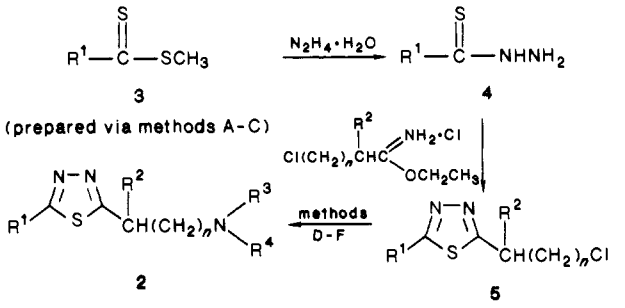


2

were synthesized in order to assess the importance of the 2′-nitrogen atom of the hydrazine group to the overall anticonvulsant profile of the series. One of the more interesting of the unsubstituted hydrazines was the 2-biphenylyl derivative (**1**, R^1 = 2-biphenylyl, R^2 = R^3 = R^4 = H), and therefore the initial target in the aminoalkyl

Scheme I



(1) Chapleo, C. B.; Myers, M.; Myers, P. L.; Smith, A. C. B.; Stillings, M. R.; Welbourn, A. P. *J. Med. Chem.* preceding paper in this issue.

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