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.

Acknowledgment. We thank Colin Edwards, Brian Gadie, Robin Pape, Ygendra Patel, and Colin Howes for their assistance in the synthetic work, members of the Pharmacology Department for their assistance in the biological testing, and Ginette Gray for typing the manuscript.

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; **6i**, 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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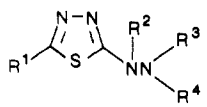
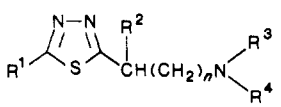
This paper describes the synthesis and pharmacological evaluation of a number of substituted 1,3,4-thiadiazoles. The first member of the series, 2-(aminomethyl)-5-(2-biphenylyl)-1,3,4-thiadiazole (**7**) was found to possess potent anticonvulsant properties in rats and mice and compared favorably with 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**)



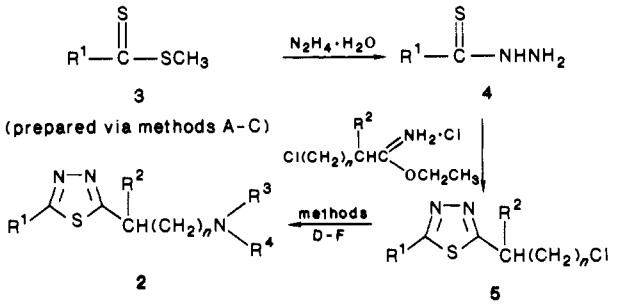
1



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.

(2) Druey, J.; Tripod, J. *Antihypertensive Agents*; Schlittler, E., Ed.; Academic Press: New York and London, 1967; p 255.

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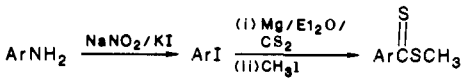
series was 2-(aminomethyl)-5-(2-biphenylyl)-1,3,4-thiadiazole (2, R^1 = 2-biphenylyl, $R^2 = R^3 = R^4 = H$, $n = 0$) (compound 7). This paper describes the synthesis and pharmacological profile of compound 7 together with a number of its close analogues.

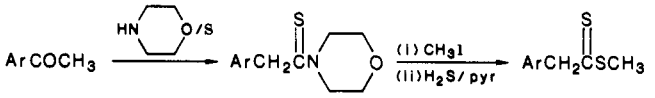
Chemistry

All of the compounds in the aminoalkyl series were prepared by the general procedure described in Scheme I. A number of synthetic pathways were available for the preparation of the dithio esters (3) and these are described below. In our hands method A was preferred for the

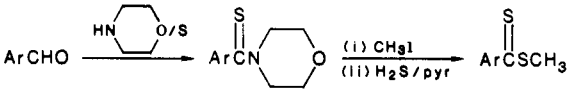
method A



method B

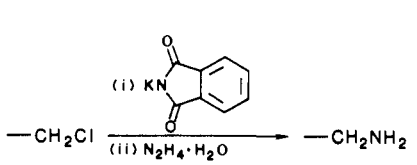


method C

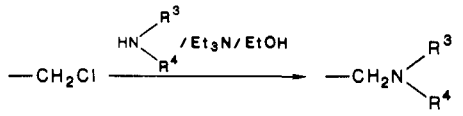


preparation of the aryl dithio esters. Synthesis of arylalkyl dithio esters was achieved in good yield via method B. Method C proved to be rather unsatisfactory, and only two dithio esters were prepared in this way. The preparation of the thiocarbonylhydrazines (4) and (chloroalkyl)thiadiazoles (5) proved to be straightforward as outlined in Scheme I. Three methods (D–F) were examined for the

method D



method E



method F

conversion of the chloroalkyl derivatives to the corresponding (aminoalkyl)thiadiazoles (2). All of the primary amines in the series were prepared via the Gabriel[3] synthesis described in method D, and this gave consistently good yields and was simple to perform. A number of attempts utilizing the Delepine[4] reaction (method F) failed. The preparation of secondary and tertiary amines was carried out by heating the (chloroalkyl)thiadiazole with the appropriate amine and triethylamine in ethanol solution.

Results and Discussion

The majority of compounds in this series contained the 2-biphenylyl moiety in the 5-position of the 1,3,4-thiadiazole ring, and this group was chosen as it conferred on the corresponding thiadiazole hydrazines[1] the best combination of potency and lack of toxicity. We found that the initial target compound in the aminoalkyl series, 2-(aminomethyl)-5-(2-biphenylyl)-1,3,4-thiadiazole (7), possessed potent anticonvulsant properties, and this result prompted the synthesis and pharmacological evaluation of the closely related derivatives (8–19, Table I). The results in the mouse metrazole (MMS) and maximal electroshock (MES) tests clearly showed that extending the side chain was deleterious in terms of potency in both screens such that the *n*-propylamino derivative (9) was devoid of anticonvulsant activity. The branched-chain derivative (10) still retained significant activity, and this was also true of compounds 11–14 in which the nitrogen atom was substituted with one or two alkyl or arylalkyl groups. Substitution with an aryl group as in compound 15 led to a complete loss of anticonvulsant activity however. The importance of the 2-biphenylyl group was emphasized by the lack of activity shown by the phenyl (6) and benzyl (18) derivatives, although it is interesting to note that the reintroduction of the 2-phenyl group into the benzyl derivative to give the biphenylylmethylene compound (19) caused a marked increase in activity in the MES test. Replacing the 2-biphenylyl moiety with 2-hexyloxyphenyl (a group that conferred good activity in the thiadiazole hydrazine series[1]) gave compounds 16 and 17, which showed some activity in the MES screen although they were slightly less potent than the lead compound 7.

More detailed studies were then carried out on compound 7. In both the rat and the mouse it was a potent anticonvulsant, blocking both electrically and chemically induced seizures. It was effective by both the intraperitoneal and oral routes, and the time of peak effect by both methods of administration was between 10 and 20 min after dosing, indicating a very rapid rate of absorption. Its potency was comparable with established anticonvulsant drugs in these tests (Tables II and III).

The rotorod was used to assess the neurotoxicity of the compound. The data in Table IV show TD_{50} values at the time of peak anticonvulsant effect obtained with compound 7 and the standard drugs after ip administration in the mouse. The protective index (PI) of the compound (TD_{50} divided by ED_{50} ip at time of peak effect) was 6.5; the corresponding values for phenytoin, phenobarbital, and carbamazepine were 7, 4.8, and 11, respectively.

The anticonvulsant profile of the aminomethyl derivative (7) is interesting as the compound is structurally dissimilar from any of the familiar anticonvulsant drugs, many of which certain ureido or amido functions. The fact that it contains an aminomethyl side chain directly linked to a heterocyclic ring has led us to speculate that its mode of action may be similar to that of muscimol, a natural product, which depresses the firing of neurons via activation of their GABA receptors.[5] However, we have no direct evidence at present that these compounds interact with GABA receptors.

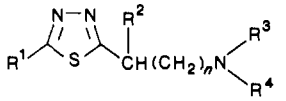
Experimental Section

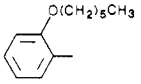
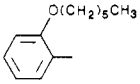
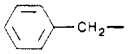
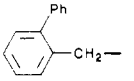
Pharmacology. Full details of the pharmacological testing procedures used in this work are described in the preceding paper.[1]

Chemistry. Melting points were determined in a Büchi apparatus in glass capillary tubes and are uncorrected. IR, NMR, and MS spectra were recorded on Perkin-Elmer 700, Varian

(3) Sheehan, J. C.; Bolhofer, W. A. *J. Am. Chem. Soc.* **1950**, *72*, 2786.
(4) Delepine, M. *Bull. Soc. Chim. Fr.* **1895**, *13*, 355.
(5) Krogsgaard-Laarsen, P. *Specific GABA Receptor Agonists and Uptake Inhibitors*; FADL'S Forlag: Kobenhavn, Arhus, and Odense, 1980; p 40.
(6) Finney, D. J. *Probit Analysis*; Cambridge University Press, Cambridge, UK, 1962.
(7) Desmedt, L. K. C.; Niemegeers, C. J. E.; Lewi, P. J.; Janssen, P. A. J. *Arzneim-Forsch. Drug Res.* **1976**, *26*, 1592.

Table I



compd	R^1	R^2	R^3	R^4	n	method of prepn	mp, °C	formula	anal.	pharmacological screening results in the mouse:[a] ED_{50}, mg/kg, po	
										metrazol	electro-shock
6		H	H	CH_3	0	A/E	212–214	$C_{10}H_{11}N_3S$·HCl	C, H, N	>200	>200
7		H	H	H	0	A/D	222–223	$C_{15}H_{13}N_3S$·HCl	C, H, N	22	20
8		H	H	H	1	A/D	156–157	$C_{16}H_{15}N_3S$·HCl·$^1/_3H_2O$	C, H, N	68	50
9		H	H	H	2	A/D	162–163	$C_{17}H_{17}N_3S$·CH_3CO_2H	C, H, N[b]	>200	>200
10		CH_3	H	H	0	A/D	174–176	$C_{16}H_{15}N_3S$·HCl	C, H, N	32	21
11		H	H	CH_3	0	A/E	210–213	$C_{16}H_{15}N_3S$·HCl	C, H, N	20	25
12		H	CH_3	CH_3	0	A/E	209–212	$C_{17}H_{17}N_3S$·HCl	C, H, N[c]	35	32
13		H	H	$CH(CH_3)_2$	0	A/E	198–200	$C_{18}H_{19}N_3S$·HCl	C, H, N	35	23
14		H	H	CH_2Ph	0	A/E	133–135	$C_{22}H_{19}N_3S$·HCl	C, H, N	29	37
15		H	H		0	A/E	153–159	$C_{22}H_{19}N_3S$·HCl	C, H, N	>200	>200
16		H	H	H	0	C/D	202–204	$C_{15}H_{21}N_3OS$·HCl	C, H, N	NT[d]	34
17		H	H	CH_3	0	C/E	155–157	$C_{16}H_{23}N_3OS$·HCl	C, H, N	NT	44
18		H	H	H	0	B/D	191–193	$C_{10}H_{11}N_3S$·HCl	C, H, N	200	110
19		H	H	H	0	B/D	176–178	$C_{16}H_{15}N_3S$·HCl	C, H, N	NT	30

[a] See Experimental Section for details of these tests. [b] C: calcd, 64.20; found, 63.67. [c] C: calcd, 61.52; found, 60.86. [d] Not tested.

Associates T-60, and Varian Associates LKB-2091 instruments, respectively, and were consistent with assigned structures. Where analyses are indicated only by symbols of the elements, results obtained were within ±0.4% of the theoretical values.

Representative examples of the procedures used in Scheme I for methods A–E will be given.

2-(Aminomethyl)-5-(biphenylyl)-1,3,4-thiadiazole (7) (Scheme I, Methods A and D). To a stirred mixture of concentrated H_2SO_4 (118 mL) and water (394 mL) was added 2-aminobiphenyl (100 g, 590 mmol). A white solid precipitated, and water (196 mL) was added. The suspension was cooled to 0–5 °C and maintained at this temperature while a solution of sodium nitrite (43.3 g, 620 mmol) in water (118 mL) was added dropwise over 1 h. The mixture was stirred for a further 0.75 h after which a solution of potassium iodide (143 g, 860 mmol) in water (788 mL) was added over 0.5 h. The mixture was stirred for 1 h at 5 °C and then allowed to warm to room temperature and extracted with dichloromethane. The organic phase was washed with 10% sodium thiosulfate solution (2 L) and water and dried. The resulting black oil was distilled at reduced pressure to give 2-iodobiphenyl: yield 121 g (73%); bp 108–115 °C (0.8 mm) [lit.[8] bp 125–126 °C (1 mm)].

The iodo compound (20.0 g, 71 mmol) was added to a stirred mixture of dry ether (75 mL) and magnesium (1.9 g, 83 mmol). After 5 min a vigorous reaction ensued. When this had subsided, the mixture was stirred at reflux for 1 h. After it had been cooled, the Grignard solution was decanted from the small quantity of

(8) Parrack, J. D.; Swan, G. A.; Wright, D. *J. Chem. Soc.* **1962**, 911.

Table II. Effect of Compound 7 on Maximal Electroshock Seizures (MES) and Maximal Metrazol Seizures (MMS) in the Mouse and Rat Compared with Phenytoin, Phenobarbital, and Carbamazepine After Oral Administration

	inhibn of hind limb tonus: ED_{50}, mg/kg, po (t = 1 h)			
	rat		mouse	
compound	MES	MMS	MES	MMS
7	10 (8–14)[a]	9 (5–12)	22 (11–14)	20 (9–27)
phenytoin	14 (6–23)	12 (9–16)	8 (4–12)	8 (6–11)
phenobarbital	9 (7–13)	4 (2–5)	12 (9–15)	4 (3–6)
carbamazepine	4 (2–7)	3 (2–5)	20 (17–23)	11 (2–16)

[a] 95% confidence limits.

Table III. Effect of Compound 7 on MES in the Mouse Compared with Phenytoin, Phenobarbital, and Carbamazepine After ip Administration

	inhibn of hind limb tonus MES ED_{50}, mg/kg, ip	
compound	MES at time of peak effect	time of peak effect, min
7	7 (5–8)[a]	10
phenytoin	8 (4–9)	60
phenobarbital	18 (13–37)	30
carbamazepine	6 (4–8)	20

[a] 95% confidence limits.

Table IV. Rotorod Test and Protective Index (PI) in the Mouse

compound	TD_{50},[a] mg/kg, po at 1 h	TD_{50}, mg/kg, ip at time of peak effect	PI[b]
7	318 (230–471)[c]	45 (23–68)	6.5
phenytoin	216 (154–339)	56 (27–74)	7
phenobarbital	68 (52–92)	86 (54–140)	4.8
carbamazepine	166 (104–282)	67 (29–108)	11.1

[a] Dose at which 50% of trained animals fall off the rotarod. [b] Protective index is calculated by dividing the TD_{50} (ip at time of peak anticonvulsant effect) by the ED_{50} under the same conditions (Table III). [c] 95% confidence limits.

magnesium remaining and added dropwise to a solution of carbon disulfide (5.0 g, 66 mmol) in dry ether (25 mL). The mixture was stirred at room temperature for 2.5 h after which methyl iodide (11.0 g, 77 mmol) in dry tetrahydrofuran (25 mL) was added over 5 min. The resultant bright-yellow suspension was stirred at reflux for 1 h; a further portion of methyl iodide (5.0 g, 35 mmol) was added and the reaction continued for 1 h. The mixture was cooled and partitioned between ethyl acetate and water. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to dryness to give methyl 2-biphenylyldithiobenzoate (**3**, R^1 = 2-biphenylyl) as a red-brown oil: yield 14.2 g (83%); IR (thin film) ν_{max} 1040, 750 cm^{-1}.

A mixture of the dithiobenzoate (14.2 g, 58 mmol) and hydrazine hydrate (98%, 11.0 g, 220 mmol) was dissolved in ethanol (100 mL) and heated at reflux for 1 h. The majority of the ethanol was then distilled off under reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give an oily solid, which was triturated with petroleum ether (bp 40–60 °C)/ether to give (2-biphenylylthiocarbonyl)hydrazine (**4**, R^1 = 2-biphenylyl) as a yellow solid: yield, 9.9 g (75%); IR ($CHBr_3$) ν_{max} 3400 cm^{-1}.

A solution of chloroacetonitrile (10.0 g, 133 mmol), ethanol (6.8 g, 148 mmol) and dry ether (76 mL) was stirred and cooled at 0 °C while a stream of dry HCl gas was bubbled through. After 0.5 h the white crystalline imidate salt had precipitated. Excess dry ether was added to the mixture, which was then filtered. The solid was washed with dry ether and stored over P_2O_5 in vacuo. The yield of imidate hydrochloride was 20.0 g (97%): mp 89 °C dec.

A mixture of the imidate salt (9.0 g, 57 mmol) and (2-biphenylylthiocarbonyl)hydrazine (9.9 g, 43 mmol) in ethanol (103 mL) was heated under reflux for 0.5 h. The ethanol was removed under reduced pressure, and the residue was partitioned between ethyl acetate and water. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give crude 2-(2-biphenylyl)-5-(chloromethyl)-1,3,4-thiadiazole (**5**, R^1 = 2-biphenylyl, n = 0) as a red solid: yield 11.3 g (91%); IR ($CHBr_3$) ν_{max} 1270, 760 cm^{-1}.

A mixture of the crude (chloromethyl)thiadiazole (1.5 g, 5.2 mmol), potassium phthalimide (0.96 g, 5.5 mmol), and dry dimethylformamide (7.5 mL) was stirred and heated at 50–70 °C for 1 h. The resulting solution was cooled and partitioned between ethyl acetate and water, and the organic layer was washed with 0.2 N NaOH and water and dried ($MgSO_4$). Evaporation gave a dark-brown gum, which was purified via column chromatography on silica eluting with chloroform to give 2-(2-biphenylyl)-5-(phthalimidomethyl)-1,3,4-thiadiazole as a light-brown solid: yield 1.0 g (63%); IR ($CHBr_3$) ν_{max} 1770, 1720 cm^{-1}.

A mixture of the phthalimide (1.0 g, 3.2 mmol), hydrazine hydrate (98%, 0.16 g, 3.2 mmol), and ethanol (7 mL) was heated under reflux. After 5 min the reaction mixture became solid; heating was continued for 0.5 h. After it had cooled, the mixture was partitioned between ether (10 mL) and aqueous KOH solution (10%, 1.0 g). The ether layer was separated off, washed with water, dried ($MgSO_4$), and evaporated to give a solid that was converted to a hydrochloride salt with use of ethanol and ethereal HCl. The resulting white solid was crystallized from ethanol/ether to give **7**: yield 0.42 g (43%); mp 222–223 °C dec. Anal. ($C_{15}H_{13}N_3S$·HCl) C, H, N.

2-(Aminomethyl)-5-(2-biphenylylmethyl)-1,3,4-thiadiazole (19) (Scheme I, Methods B and D). A suspension of 2-biphenylylmagnesium iodide [prepared from 2-iodobiphenyl (51.0 g, 182 mmol), magnesium (4.5 g, 196 mmol), and dry ether (180 mL)] was added portionwise to a vigorously stirred mixture of acetic anhydride (75 mL, 740 mmol) and dry ether (100 mL) at 5–10 °C over 0.75 h. The mixture was stirred at this temperature for 0.5 h after which a saturated solution of ammonium chloride was added, and the resultant mixture was extracted with ether. The combined ether layers were washed with water and 2 N HCl, dried, and evaporated to give a dark-red oil, which was distilled under reduced pressure to give 2-acetylbiphenyl: yield 23.0 g (64%); bp 125–130 °C (1.5 mm) [lit.[9] bp 104–105 °C (1.0 mm)]. This was converted to the corresponding dithio ester as described below. No attempts were made to purify or analyze the intermediates.

A mixture of 2-acetylbiphenyl (23.0 g, 117 mmol), morpholine (15.5 g, 178 mmol), and sulfur (5.7 g, 178 mmol) was heated at reflux for 3 h. The cooled solution was partitioned between ethyl acetate and 2 N HCl, and the organic layer was separated off, washed with water, dried ($MgSO_4$), and evaporated to give 2-biphenylylacetothiomorpholide as a deep-red oil: yield 30.6 g (88%).

A solution of the acetothiomorpholide (30.6 g, 103 mmol), methyl iodide (14.4 g, 101 mmol), and acetone (50 mL) was allowed to stand at room temperature for 30 h. The crystalline quaternary iodide salt that had precipitated was filtered, washed with ether and ethyl acetate, and dried: yield 20.1 g (44%).

Hydrogen sulfide gas was passed through a suspension of the quaternary salt (20.1 g, 46 mmol) in dry pyridine (100 mL) at 0 °C. After 0.5 h, a clear solution had formed that was poured into excess 2 N HCl and extracted with ether. The organic layer was washed with water, dried ($MgSO_4$), and evaporated to give methyl 2-biphenylyldithioacetate (**3**, R^1 = 2-biphenylylmethyl) as a pale-yellow mobile oil: yield, 7.9 g (67%).

The dithioacetate was converted to thiadiazole **19** by using the method described in the synthesis of compound **7** from the corresponding dithiobenzoate (method D): yield 9.5%.

2-[2-(Hexyloxy)phenyl]-5-[(methylamino)methyl]-1,3,4-thiadiazole (17) (Scheme I, Methods C and E). Salicylaldehyde (100 g, 820 mmol) was added dropwise to a solution of potassium hydroxide (45.8 g, 818 mmol) in methanol (1 L) at room temperature. Hexyl bromide (135.2 g, 819 mmol) was then added dropwise, and the stirred mixture was heated under reflux for 65 h. The methanol was evaporated off under reduced pressure, and the residue was partitioned between water and ether. The ether layer was washed with 2 N NaOH solution, water, and brine,

(9) Bernstein, S.; Dorfman, L. *J. Am. Chem. Soc.* **1946**, *68*, 1663.

dried ($MgSO_4$), and evaporated to give, as a colorless oil, 2-(hexyloxy)benzaldehyde: yield 124.9 g (74%); IR (thin film) ν_{max} 1700 cm^{-1}.

A mixture of the aldehyde (39.7 g, 193 mmol), morpholine (25.5 g, 293 mmol), and sulfur (9.2 g, 288 mmol) was heated under reflux for 60 h. After it had been cooled, it was dissolved in ethyl acetate and the solution was washed with 2 N HCl solution and water and dried ($MgSO_4$). Evaporation of the organic layer gave crude 2-(hexyloxy)benzothiomorpholide as a dark-red oil: yield, 55.6 g (94%); IR (thin film) ν_{max} 1470, 1230 cm^{-1}.

The thiomorpholide was then converted to the corresponding dithiobenzoate (**3**, R^1 = 2-(hexyloxy)phenyl) in the same manner as that described in the synthesis of the 2-biphenylylmethyl derivative (**3**, R^1 = 2-biphenylylmethyl) (method B): yield 94%. The dithiobenzoate was converted to the chloromethyl derivative (**5**, R^1 = 2-(hexyloxy)phenyl, n = 0) by using the method described in the synthesis of the corresponding 2-biphenylyl derivative (**5**, R^1 = 2-biphenylyl, n = 0) (Scheme I): yield 62%.

A mixture of 2-(chloromethyl)-5-[2-(hexyloxy)phenyl]-1,3,4-thiadiazole (2.2 g, 7.1 mmol), methylamine (4.13 g, 133 mmol), and ethanol was heated at 55–60 °C for 2.5 h. The solution was evaporated under reduced pressure, and the residue was partitioned between ethyl acetate and 2 N HCl solution. The aqueous layer was washed with ethyl acetate, basified with 2 N NaOH solution, and extracted with ethyl acetate. The organic phase was washed with water, dried ($MgSO_4$), and evaporated to give a red solid. This was dissolved in ethanol, and ethereal HCl was added. The resulting hydrochloride salt was filtered off and crystallized from ethanol/ether to give **17**: yield 0.4 g (17%); mp 155–157 °C. Anal. ($C_{16}H_{23}N_3OS$·HCl) C, H, N.

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Registry No. **2** (R^1 = 2-biphenylyl, R^2 = H, R^3 = R^4 = phthalimide, n = 0), 104090-72-4; **3** (R^1 = 2-biphenylyl), 104090-69-9; **3** (R^1 = 2-biphenylylmethyl), 104090-75-7; **3** (R^1 = 2-(hexyloxy)phenyl), 104090-77-9; **4** (R^1 = 2-biphenylyl), 104090-70-2; **5** (R^1 = 2-biphenylyl, R^2 = H, n = 0), 104090-71-3; **5** (R^1 = 2-(hexyloxy)phenyl, R^2 = H, n = 0), 104090-78-0; **6**, 104090-42-8; **6** (free base), 104090-56-4; **7**, 104090-43-9; **7** (free base), 104090-57-5; **8**, 104090-44-0; **8** (free base), 104090-58-6; **9**, 104090-46-2; **9** (free base), 104090-45-1; **10**, 104090-47-3; **10** (free base), 104090-59-7; **11**, 104090-48-4; **11** (free base), 104090-60-0; **12**, 104090-49-5; **12** (free base), 104090-61-1; **13**, 104090-50-8; **13** (free base), 104090-62-2; **14**, 104090-51-9; **14** (free base), 104090-63-3; **15**, 104090-52-0; **15** (free base), 104090-64-4; **16**, 104090-53-1; **16** (free base), 104090-65-5; **17**, 104090-54-2; **17** (free base), 104090-66-6; **18**, 104090-55-3; **18** (free base), 104090-67-7; **19**, 104113-70-4; **19** (free base), 104090-68-8; HN=C(OEt)-CH_2Cl·HCl, 36743-66-5; 2-aminobiphenyl, 90-41-5; 2-iodobiphenyl, 2113-51-1; chloroacetonitrile, 107-14-2; 2-acetylbiphenyl, 2142-66-7; 2-biphenylacetothiomorpholide, 104090-73-5; 2-biphenylylacetothiomorpholide methiodide, 104090-74-6; salicylaldehyde, 90028; hexyl bromide, 111-25-1; 2-(hexyloxy)benzothiomorpholide, 104090-76-8; 2-(hexyloxy)benzaldehyde, 7162-59-6.

Structure–Activity Studies of 4,6-Disubstituted 2-(Morpholinocarbonyl)furo[3,2-*b*]indole Derivatives with Analgesic and Antiinflammatory Activities

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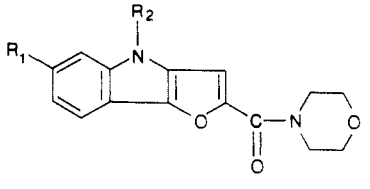
4,6-Disubstituted 2-(morpholinocarbonyl)furo[3,2-*b*]indole derivatives showed analgesic and antiinflammatory activities when assayed by the acetic acid writhing test in mice and the carrageenin edema test in rats. To understand how the substituents affect the biological activities, the quantitative structure–activity relationships (QSAR) of 38 compounds were analyzed using the adaptive least-squares method (ALS method). The resulting QSAR suggested that some chemical modifications of 4,6-disubstituted furo[3,2-*b*]indole derivatives would improve their biological activities. Thus, 15 additional compounds were synthesized to reinforce and confirm the correlation. Among these compounds, particularly 4-(2-ethylhexanoyl)-2-(morpholinocarbonyl)-6-(trifluoromethyl)furo[3,2-*b*]indole showed pronounced biological activities. This compound gave a pharmacological activity spectrum similar to that of tiaramide but exhibited much higher potency.

The structure of the furo[3,2-*b*]indole skeleton is of particular interest in connection with its possible relationship with biological activity. In a previous paper[1] we reported the synthesis and analgesic and antiinflammatory activities of 4-(alkoxycarbonyl)-2-(morpholinocarbonyl)-furo[3,2-*b*]indole derivatives I. When structure–activity



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relationships of the derivatives were considered, it appeared that CF_3 and Cl as substituent R_1 were associated with an increase in the potency. Although the effect of substituent R_2 seemed rather complicated, a bulky substituent (R_2) tended to enhance the analgesic and antiinflammatory activities. This consideration prompted us to attempt a quantitative structure–activity analysis to develop more potent compounds.

This paper described the analysis of the quantitative structure–activity relationships (QSAR) of these derivatives for analgesic and antiinflammatory activities using the adaptive least-squares (ALS) method[2-4] and the design

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