New Dibenzothiadiazepine Derivatives with Antidepressant Activities

Danilo Giannotti,*^{,†} Giovanni Viti,[†] Piero Sbraci,[†] Vittorio Pestellini,[†] Giovanna Volterra,[‡] Franco Borsini,[‡] Alessandro Lecci,[‡] Alberto Meli,[‡] Paolo Dapporto,[§] and Paola Paola[§]

Dipartimento Ricerche Chimiche e Farmacologiche, A. Menarini Industrie Farmaceutiche Riunite S.r.l., V. Sette Santi 3, 50131 Firenze, Italy, and Dipartimento di Energetica, Università di Firenze, V.S. Marta 3, 50139 Firenze, Italy. Received October 11, 1989

A new series of 11-[(aminoalkyl)carbonyl] derivatives of 6,11-dihydrodibenzo[c,f][1,2,5]thiadiazepine 5,5-dioxide (10-39) were synthesized and evaluated for potential antidepressant activity in the apomorphine-induced hypothermia (Apo 16) test. Effects on reserpine-induced hypothermia and toxicity for the most potent antagonists of Apo 16 hypothermia were also studied. Structure-activity relationships are reported. Anticholinergic effects were evaluated for compound 12, identified as the most potent and least toxic in this series, by assessing physostigmine lethality. Compound 12 was also subjected to X-ray analysis.

Introduction

Many antidepressant agents used in clinical practice have a tricyclic structure, with two aromatic rings fused to the central heptatomic ring. An aminoalkyl side chain is attached to the central ring on which one or more heteroatoms can be present.

This paper describes tricyclic compounds where three heteroatoms, a sulfonamido group, and a nitrogen atom are present in the heptatomic ring as in the dibenzo-thiadiazepines shown in Schemes I and II. Some derivatives of dibenzothiadiazepines with an aminoalkyl chain in position 11 have been reported.^{1,2} These compounds were shown to have imipramine-like activity in animal models of depression but were not developed due to adverse reactions on the cardiovascular system.³

With the aim of finding a potential antidepressant with fewer side effects than the classical tricyclic antidepressants,⁴ we synthesized new dibenzothiadiazepines substituted in position 11 with an (aminoalkyl)carbonyl chain;⁵ the introduction of a carbonyl linked to nitrogen in position 11 transforms this basic nitrogen to an amide and therefore may change the pharmacological and toxicological properties of the compounds.

It is known that in imipramine and desipramine, an analogous substitution of the aminoalkyl chain with an (aminoalkyl)carbonyl chain gives rise to products with antidepressant activity;^{6,7} in other cases with the same substitution no pharmacological activity was found.⁸ No information is given on the effects on toxicity for this substitution, however.

It is noteworthy that tianeptine (example I), a new atypical antidepressant which also has an heptatomic ring containing the sulfonamido group in position 5–6, has few side effects and is active as an antidepressant in clinical trials.⁹⁻¹¹



Chemistry

The 6,11-dihydrodibenzo[c,f][1,2,5]thiadiazepine 5,5dioxide 7a-l intermediates¹² listed in Table I were pre-

[†]Dipartimento Ricerche Chimiche, A. Menarini Industrie Farmaceutiche.

- [‡]Dipartimento Ricerche Farmacologiche, A. Menarini Industrie Farmaceutiche.
 - [§]Dipartimento di Energetica, Università di Firenze.

pared by the general procedures outlined in Scheme I.

The reaction of the 2-nitrobenzenesulfonyl chlorides 1 with 2-haloanilines 2 led to the N-(2'-halophenyl)-2nitrobenzenesulfonamides 3a-i; subsequent reduction with boiling Fe/AcOH and acetylation in situ with Ac₂O gives N-(2-halophenyl)-2-(acetylamino)benzenesulfonamides 5a-j. Alternatively, these compounds could be directly obtained by treatment of the 2-aminobenzenesulfonyl chlorides 1a with 2 followed by acetylation with Ac₂O. Compounds 5a-j were N-alkylated to N-(2'-halophenyl)-N-alkyl-2-(acetylamino)benzenesulfonamides 6a-1and cyclized, according to the method of Goldberg,¹³ to products 7a-1.

The 11-[(aminoalkyl)carbonyl] derivatives of 6,11-dihydrodibenzo[c,f][1,2,5]thiadiazepine 5,5-dioxide 10-39⁵ were synthesized as outlined in Scheme II and are summarized in Table II. Refluxing compounds 7a-1 with excess of ω -chloroalkanoyl chlorides gave derivatives 9a-m for n = 1 or 2 (listed in Table I). Treatment of these derivatives with amines afforded the desired products 12-38.

Compound 39 was obtained by catalytic reduction of the azido derivative obtained from compound 9a.

Products 10 and 11 were synthesized by reaction of the sodium salt of 7a with trichloromethyl chloroformate and subsequent treatment of the intermediate 8a with ammonia to form 10 or with dimethylamine to form 11.

Results and Discussion

Data relative to the antagonism of apomorphine (16 mg/kg) induced hypothermia by the new compounds (400 mg/kg os) are presented in Table II.

The data indicate that the amino group in the (amino-

- Weber, A. U.S. Patent 3,274,058, 1966; Chem. Abstr. 1967, 66, 95092.
- (2) Kreighbaum, W. E. U.S. Patent 3,322,789, 1967; Chem. Abstr. 1967, 67, 100161.
- (3) Weber, A.; Frossard, J. Ann. Pharm. Fr. 1966, 24, 445.
- (4) For a review on "second-generation antidepressants", see: Blackwell, B.; Simon, J. S. Drugs Today 1986, 22, 611.
- (5) Borsini, F.; Meli, A.; Volterra, G.; Giannotti, D.; Pestellini, V. Ital. Patent. 1988, 9466.
- (6) Oksenkrug, G. F. Farmakol. Toksikol. 1975, 38, 23.
- (7) Oksenkrug, G. F. J. Pharm. Pharmacol. 1973, 25, 1013.
- (8) Monro, A. M.; Quinton, R. M.; Wrigley, T. I. J. Med. Chem. 1963, 6, 255.
- (9) Labrid, C.; Moleyre, J.; Poignant, J. C.; Malen, C.; Mocaer, E.; Kamoun, A. Clin. Neuropharmacol. 1988, 11 (Suppl. 2), 21.
- (10) Mocaer, E.; Rettori, M. C.; Kamoun, A. Clin. Neuropharmacol. 1988, 11 (Suppl. 2), 32.
- (11) Defrance, R.; Marey, C.; Kamoun, A. Clin. Neuropharmacol. 1988, 11 (Suppl. 2), 74.
- (12) Weber, A. U.S. Patent 3,268,557, 1966; Chem. Abstr. 1966, 65, 15406.
- (13) (a) Goldberg, I. Ber. Dtsch. Chem. Ges. 1906, 39, 1691. (b) Goldberg, I. Ber. Dtsch. Chem. Ges. 1907, 40, 4541.

Scheme I



alkyl)carbonyl chain is important for the antagonism of apomorphine-induced hypothermia. The terminal amino group of the most active compounds can be secondary (29) or tertiary and linked to a short chain alkyl group (12, 21, 23, 29, 33, 34, 36, 38); decrease in activity can be observed for bulkier or branched alkyl groups (17, 24, 25) and in the absence of the alkyl group (39). Compounds 13-16, 19, 20, and 26-28, where the amino group is part of a heterocycle, were inactive. When bulkier alkyl groups are substituted for the methyl group on the sulfonamide nitrogen (position 6) compounds (22, 32) with lower activity are obtained.

Aromatic substitution in the two benzene rings, in compounds with the dimethylamino group in the side chain, gives compounds (33, 34, 36, 38) with comparable activity to the unsubstituted compound (12) or compounds (18, 30, 31, 35, 37) with lower activity.

The ED_{50} for reversal of Apo 16 induced hypothermia and the minimal dose effective in reducing reserpine-induced hypothermia, as well as the LD_{50} for the more active compounds, are shown in Table III. Imipramine and compounds 40 and 41 (dibenzothiadiazepines which have an aminoalkyl chain substituted on position 11 of the central ring)³ were used for comparison.

With the exception of 33 and 38 most of the compounds selected had similar efficacy in antagonizing apomorphine-induced hypothermia, while compound 12 was the most active in antagonizing reserpine-induced hypothermia. Some activity in the reserpine test was seen with compounds 29 (a derivative with a secondary terminal amino group) and 34 (a derivative with a methyl aromatic substitution in position 9).

Aromatic substitution (33, 34, 36, 38) caused a decrease in the activity in antagonizing reserpine-hypothermia in comparison with compound 12.

Compound 12 shows that the amino group of the (aminoalkyl)carbonyl chain with the best activity is the dimethylamino group, while compound 29 with the monomethylamino group is more toxic and is also less potent than the dimethylamino compounds (12) in reversing reserpine-induced hypothermia. Compound 23 with the diethylamino group has about half the activity of compound 12 in the reversal of Apo 16 induced hypothermia and has reduced potency in reversing reserpine-induced hypothermia even though it seems to be somewhat less toxic.

The length of the side chain for optimal activity in this series seems to be that where the two nitrogen atoms are separated by a chain of two carbon atoms (12); when the chain is of three carbon atoms, activity decreases (21). This fact is in contrast to what is seen with other imipramine-like compounds, where the side chain is usually of three carbon atoms.

In the dibenzothiadiazepines with a two-carbon side chain, the introduction of a carbonyl group linked to a Scheme II



Table I. Physical Properties of Dibenzothiadiazepines 7a-l and 9a-m



no.	R ₁	R ₂	R ₃	R ₄	formulaª	mp, °C (solv) ^b	% yield
7a	CH _a	Н	н	Н	$C_{13}H_{12}N_2O_2S$	201-202 (E) ^c	91
7b	CH_3	2-Cl	H	Н	$C_{13}H_{11}CIN_2O_2S$	308-310 (P)	78
7c	CH ₃	2-OCH ₃	н	Н	$C_{14}H_{14}N_2O_3S$	187-189 (E)	58
7d	CH_{3}	2-CF ₃	н	Н	$C_{14}H_{11}F_{3}N_{2}O_{2}S$	231–232 (E)	65
7e	CH_3	Н	9-Cl	Н	$C_{13}H_{11}CIN_2O_2S$	265 dec. (E)	55
7f	CH ₃	Н	9-CH ₃	Н	$C_{14}H_{14}N_2O_2S$	259-260 (A)	62
7g	CH_3	н	8-Cl	Н	$C_{13}H_{11}CIN_2O_2S$	225-226 (E)	68
7ĥ	CH ₃	2-CH ₃	н	Н	$C_{14}H_{14}N_2O_2S$	167-169 (P)	88
7i	CH ₃	3-C1	н	Н	$C_{13}H_{11}CIN_2O_2S$	267-269 (P)	63
7j	CH ₃	2-Cl, 3-CH ₃	н	Н	$C_{14}H_{13}ClN_2O_2S$	243-244 (E)	72
7k	C₂H ₅	Н	н	Н	$C_{14}H_{14}N_2O_2S$	188–189 (E)	60
71	C_3H_7	Н	н	Н	$C_{15}H_{16}N_2O_2S$	186–187 (E)	60
9a	CH ₃	Н	н	COCH ₂ Cl	$C_{15}H_{13}ClN_2O_3S$	141–143 (L)	80
9b	CH ₃	2-Cl	н	COCH ₂ Cl	$C_{15}H_{12}Cl_2N_2O_3S$	183–184 (L)	85
9c	CH ₃	2-OCH ₃	н	COCH ₂ Cl	$C_{16}H_{15}CIN_2O_4S$	178–179 (E)	73
9d	CH ₃	2-CF ₃	н	COCH ₂ Cl	$C_{16}H_{12}ClF_3N_2O_3S$	121–122 (E)	76
9e	CH ₃	H	9-Cl	COCH ₂ Cl	$C_{15}H_{12}Cl_2N_2O_3S$	202–203 (A)	70
9f	CH_3	H	9-CH ₃	COCH ₂ Cl	$C_{16}H_{15}ClN_2O_3S$	155–157 (A)	80
9g	CH ₃	H	8-C1	COCH ₂ Cl	$C_{15}H_{12}Cl_2N_2O_3S$	158–159 (L)	86
9h	CH_3	$2-CH_3$	н	COCH ₂ Cl	$C_{16}H_{15}ClN_2O_3S$	167–168 (A)	72
9i	CH ₃	3-C1	Н	COCH ₂ Cl	$C_{15}H_{12}Cl_2N_2O_3S$	209–210 (A)	90
9j	CH ₃	2-Cl, 3-CH ₃	н	COCH ₂ Cl	$\mathbf{C_{16}H_{14}Cl_2N_2O_3S}$	164-166 (E)	70
9k	C_2H_5	H	н	COCH ₂ CI	$C_{16}H_{15}CIN_2O_3S$	174-176 (E)	75
91	C_3H_7	H	H	COCH ₂ CI	$C_{17}H_{17}CIN_2O_3S$	147-148 (L)	72
9m	CH ₃	н	н	COCH ₂ CH ₂ Cl	$C_{16}H_{15}CIN_2O_3S$	131–132 (E)	80

^a Compounds were analyzed for C, H, and N, and results were within $\pm 0.4\%$ of the theoretical values. ^bRecrystallization solvents: A = acetone, E = ethanol, L = ethyl acetate, P = 1-propanol. ^cReference 3.

nitrogen in position 11 in the side chain increases overall activity in reversing apomorphine and reserpine hypothermia, and above all brings about a reduction in toxicity. Finally, compound 12 of this series is the compound with the best therapeutic index, when compared to 40, 41, and imipramine.

Further studies on anticholinergic activity, cardiotoxicity, binding, and mechanism of action of this tricyclic

Table II. Physical and Pharmacological Data for 11-(Aminoalkyl)carbonyl Derivatives of Dibenzothiadiazepine



									apomorphine
			-		~		60 (1) b	.%	test: rectal
no.	n	NRR'	R ₁	R ₂	R	formula"	mp, °C (solv)°	yield	temperature, °C
10	0	NH ₂	CH3	н	н	$C_{14}H_{13}N_3O_3S$	240-242 (A)	60	33.8
11	0	$N(CH_3)_2$	CH3	н	н	$C_{16}H_{17}N_{3}O_{3}S$	170–171 (E)	50	33.7
12	1	$N(CH_3)_2$	CH_3	н	Н	$C_{17}H_{19}N_3O_3S$	179–181 (E)	70	38.7*
13	1	4-methylpiperazin-1-yl	CH_3	2-Cl,3-CH ₃	н	$C_{21}H_{25}ClN_4O_3S$	156-158 (I)	73	32.5
14	1	4-phenylpiperazin-1-yl	CH ₃	2-Cl,3-CH ₃	Н	$C_{26}H_{27}ClN_4O_3S$	194-196 (A)	66	34.5
15	1	4-(2-hydroxyethyl)piperazin-1-yl	CH ₃	2-Cl,3-CH ₃	н	C ₂₂ H ₂₇ ClN ₄ O ₄ S·2HCl	234-236 (E)	63	34.1
16	1	4-(2-pyrimidyl)piperazin-1-yl	CH ₃	2-Cl,3-CH ₃	Н	$C_{24}H_{25}ClN_6O_3S$	180-182 (T/R)	60	32.7
17	1	NHCH(CH ₃) ₂	CH ₃	2-Cl,3-CH ₃	н	C ₁₉ H ₂₂ ClN ₃ O ₃ S-HCl	248–250 (A)	50	33.1
18	1	N(CH ₃) ₂	CH ₃	2-Cl,3-CH ₃	н	C ₁₈ H ₂₀ ClN ₃ O ₃ S·HCl	240-242 (E)	80	35.8
19	1	4-methylpiperazin-1-yl	CH ₃	Н	н	$C_{20}H_{24}N_4O_3S$	143-144 (I)	70	34.4
20	1	4-(2-hydroxyethyl)piperazin-1-yl	CH ₃	н	н	C ₂₁ H ₂₈ N ₄ O ₄ S·2HCl	236–238 (E)	60	34.4
21	2	$N(CH_3)_2$	CH ₃	н	н	C ₁₈ H ₂₁ N ₃ O ₃ S-HCl	189-190 (A)	68	36.5*
22	1	$N(CH_3)_2$	C_2H_5	H	н	$C_{18}H_{21}N_3O_3S$	115-116 (C)	20	35.1
23	1	$N(C_2H_5)_2$	CH ₃	н	н	$C_{19}H_{23}N_3O_3S$	161-162 (E)	67	37.4*
24	1	NHCH(CH ₃) ₂	CH_3	н	н	$C_{18}H_{21}N_3O_3S$	115–117 (E)	60	34.1
25	1	NHC(CH ₃) ₃	CH_3	н	Н	$C_{19}H_{23}N_3O_3S$	143-144 (E)	64	32.2
26	1	morpholin-1-yl	CH_3	н	н	$C_{19}H_{21}N_{3}O_{4}S$	129–131 (C)	70	33.9
27	1	4-methylpiperidin-1-yl	CH_3	н	Н	$C_{21}H_{25}N_3O_3S$	159-160 (E)	61	33.2
28	1	pyrrolidin-1-yl	CH_3	н	Н	$C_{19}H_{21}N_{3}O_{3}S$	175–177 (E)	67	34.2
29	1	NHCH ₃	CH_3	н	н	$C_{16}H_{17}N_{3}O_{3}S$	135–137 (L)	45	38.2*
30	1	$N(CH_3)_2$	CH_3	2-C1	Н	$C_{17}H_{18}CIN_3O_3S$	138–139 (I)	75	35.4
31	1	$N(CH_3)_2$	CH_3	$2-OCH_3$	н	C ₁₈ H ₂₁ N ₃ O ₄ S·HCl	270–272 (E)	70	33.6
32	1	$N(CH_3)_2$	C_3H_7	н	н	C ₁₉ H ₂₃ N ₃ O ₃ S⋅HCl	147–149 (I)	77	35.8
33	1	$N(CH_3)_2$	CH_3	н	9-Cl	$C_{17}H_{18}CIN_3O_3S$	175–176 (P)	70	37.4*
34	1	$N(CH_3)_2$	CH_3	н	$9-CH_3$	$C_{18}H_{21}N_{3}O_{3}S$	135–137 (E)	78	38.8*
35	1	$N(CH_3)_2$	CH_3	$2-CF_3$	H	$C_{18}H_{18}F_{3}N_{3}O_{3}S$	156-157 (I)	63	34.8
36	1	$N(CH_3)_2$	CH_3	н	8-Cl	$C_{17}H_{18}ClN_3O_3S$	132–133 (I)	82	39.5*
37	1	N(CH ₃) ₂	CH_3	$2-CH_3$	н	$C_{18}H_{21}N_3O_3S$	159–160 (I)	74	35.2
38	1	$N(CH_3)_2$	CH₃	3-Cl	н	C ₁₇ H ₁₈ ClN ₃ O ₃ S·HCl	163-165 dec (I)	65	37.7*
39	1	NH ₂	CH_3	н	Н	$C_{15}H_{15}N_3O_3S$ ·HCl	242-244 (I)	46	36.1

^a Compounds were analyzed for C, H, and N, and results were within $\pm 0.4\%$ of the theoretical values. ^bRecrystallization solvents: A = acetone, C = cyclohexane, E = ethanol, I = 2-propanol, L = ethyl acetate, T = tetrahydrofuran, R = ethyl ether, P = 1-propanol. ^cValues of rectal temperature represent the mean from 8-10 mice. The standard errors (omitted) were in the range of 1-3% of the mean. Compounds were administered orally at a dose of 400 mg/kg 0.5 h before the rectal temperature measurement. Apomorphine (16 mg/kg) was injected subcutaneously 30 min before the rectal temperature recording. The rectal temperature of vehicle- and apomorphine-treated mice ranged from 36.7 to 37.2 and from 33 to 34 °C, respectively. * P < 0.01 from rectal temperature of apomorphine-treated mice.

with potential antidepressant activity were therefore carried out.

Since anticholinergic side-effects are known to be very common with tricyclic antidepressants,¹⁴ the effect of compound 12, imipramine, and amitriptyline on physostigmine lethality were compared (Table IV). Results clearly indicate that compound 12 has far less anticholinergic effects than imipramine and amitriptyline. Tricyclic antidepressants have direct myocardial effects due to high affinity for cardiac tissue. Cardiac activity is reflected by electrocardiographic changes and changes in contractile activity.¹⁴ Compound 12 was compared to imipramine in its effects on heart rate both in vivo and in vitro and on the R/S ratio in the ECG. It had far less cardiotoxicity than imipramine.¹⁵

It is interesting that as far as binding studies for com-

⁽¹⁵⁾ Borsini, F.; Volterra, G.; Lecci, A.; Evangelista, S.; Mancinelli, A.; Cutrufo, C.; Parlani, M.; Mennini, T.; Barone, D.; Meli, A. Arzneim.-Forsch., in press.



Figure 1. ORTEP drawing of 12.

pound 12 are concerned, binding was not found to any of the various receptors examined (α - and β -adrenergic, do-

⁽¹⁴⁾ Baldessarini, R. J. In *The Pharmacological Basis of Therapeutic*, 7th ed.; Gilman, A. G., Goodman, L. S., Rall, T. W., Murad, F., Eds.; MacMillan Publishing Co.: New York, 1985; Chapter 19.

Table III. Pharmacological Results for Representative 11-[(Aminoalkyl)carbonyl] Derivatives of Dibenzothiadiazepine



				hypothern		
no.	R4	R_2	R_3	ED ₅₀ Apo 16 ^a	minimal effective dose: reserpine test ^b	LD ₅₀ °
12	COCH ₂ N(CH ₃) ₂	Н	Н	13.5 (4.1-22.6)	25	1920 (1802-2064)
21	COCH ₂ CH ₂ N(CH ₃) ₂	Н	Н	23.1 (11.3-94.9)	>100	521 (374-726)
23	COCH ₂ N(C ₂ H ₅) ₂	н	н	23 (3.4-71.1)	>100	>2000 ^d
29	COCH ₂ NHCH ₃	Н	н	12 (1.2-22.2)	100	789 (613–1015)
33	COCH ₂ N(CH ₃) ₂	Н	9-Cl	50.6 (34-98.6)	>100	NT ^e
34	$COCH_2N(CH_3)_2$	H	9-CH ₃	14.4 (10.2-24.7)	100	1734 (1525–1972)
36	COCH ₂ N(CH ₃) ₂	н	8-C1	23.5 (15.3-43.9)	>100	1424 (1136–1785)
38	COCH ₂ N(CH ₃) ₂	3-Cl	н	54.5 (26.1-102.2)	>100	NT
40	CH ₂ CH ₂ N(CH ₃) ₂	н	н	>100	100	468 (387–564)
41	CH ₂ CH ₂ CH ₂ N(CH ₃) ₂	Н	н	4.9 (1.3-11.1)	>100	655 (542-792)
	imipramine			3.7 (1.1-4.8)	4	343 (263-448)

^aSee legend of Table II for apomorphine test. ED_{50} : dose of compound reducing apomorphine-induced hypothermia by 50%; 95% confidence limits are reported in brackets. ^bReserpine (2.5 mg/kg) was administered subcutaneously 18 h before the rectal-temperature recording. Compounds were given orally at time of peak activity in general 0.5 h before rectal-temperature recording. ^cLD₅₀: dose of compound in mg/kg inducing lethality in 50% of mice after 14 days; 95% confidence limits are reported in parentheses. ^d 30% at 2 g/kg. ^sNT: not tested.

Table IV. Effect of Compound 12, Imipramine, and Amitriptyline on Physostigmine-Induced Lethality

treatment	dose, mg/kg	physostigmine, % of lethalityª	
vehicle	<u></u>	100	_
compound 12	200	95	
compound 12	400	95	
compound 12	600	90	
amitriptyline	25	37*	
imipramine	50	67*	
imipramine	25	95	

^aCompounds were orally administered 60 min before physostigmine (0.9 mg/kg) intraperitoneal injection. Lethality was evaluated 24 h later. * $P < 0.01 (\chi^2)$ vs vehicle.

pamine, serotonin, histamine, benzodiazepine, GABA, muscarinic, imipramine, and desipramine).¹⁵ Similar results were found for tianeptine.¹⁶

Unlike imipramine, compound 12 does not inhibit 5HT or NA uptake,¹⁵ on the contrary, like tianeptine,¹⁷ compound 12 enhances 5HT uptake.¹⁵

In addition to the above, conformational studies were carried out for compound 12; in Figure 1 an ORTEP view of the structure as determined by X-ray analysis is shown.

There are some structural characteristics that are analogous to those of the classical tricyclic antidepressants: (1) The dihedral angle between the two benzene rings is 124°, this is important as the average folding angle is about 120° in antidepressants while it is 155° in neuroleptics.¹⁸

(2) The (aminoalkyl)carbonyl chain lies in the opposite direction to the tricyclic arrangement and displays a conformation close to the trans one: the dihedral angle N2-C7-C8-N3 is 170.7 (9)°. This arrangement of the side chain is found in X-ray analysis of imipramine and in other tricyclic antidepressants.^{19,20}

- (16) Kato, G.; Weitsch, A. F. Clin. Neuropharmacol. 1988, 11, S43.
 (17) Mennini, T.; Mocaer, E.; Garattini, S. Naunyn-Schmiedeberg's Arch. Pharmacol. 1987, 336, 478.
- Arch. Pharmacol. 1987, 336, 478. (18) Pepe, G.; Reboul, J. P.; Cristan, B. Eur. J. Med. Chem. 1989,

(3) The distance of the nitrogen N3 of the side chain to the center of the nearest ring is 5.15 Å. A similar distance was found in the correlation analysis of conformations of classical tricyclic antidepressants (5-5.5 Å),²¹ whereas a different distance (6-7 Å) was found for the energetically favored conformations of pirenzepine, a tricyclic compound devoid of antidepressant activity.²²

Compound 12, however, also presents some features which are characteristic of this product: the geometry around the N2 atom shows an sp² hybridization for this atom, this feature is indicative of a large conjugation of the double bond in the N2-C7-O3 moiety; the presence of intramolecular hydrogen bonds as C9-H91...O3 (the H91---O3 distance is 2.62 Å), C15-H15---O1 (the H15---O1 distance is 2.60 Å), and C17-H171-O1 (the H171-O1 distance is 2.22 Å) stabilize the molecular conformation. Some intermolecular hydrogen bonds that involve the O2 and the O3 oxygen atoms are present. This conformational study of compound 12, shows that there are important structural similarities with classical antidepressant tricyclics. Compound 12, and other tricyclic antidepressants also have the same profile of activity in the apomorphine test.23

In spite of these structural and pharmacological analogies, the fact that compound 12, unlike other tricyclic antidepressants, does not inhibit monoamine uptake could indicate that if a common mechanism exists, some other biochemical property, shared by tricyclic antidepressants, could be important for antidepressant activity.

In any case further conformational and structural studies are necessary to try to better elucidate similarities and

- (20) Andrews, P. R.; Lloyd, E. J. Med. Res. Rev. 1982, 2, 355.
- (21) De Paulis, T.; Kelder, D.; Ross, S. B. Mol. Pharmacol. 1978, 14, 596.
- (22) Trummlitz, G.; Schmidt, G.; Wagner, H. U.; Luger, P. Arzneim.-Forsch. 1984, 34, 849.
- (23) Puech, A. J.; Chermat, R.; Poncelet, M.; Doaré, L.; Simon, P. Psychopharmacology 1981, 75, 84.

⁽¹⁸⁾ Pepe, G.; Reboul, J. P.; Cristan, B. Eur. J. Med. Chem. 1989, 24, 1.

⁽¹⁹⁾ Tollenaere, J. P.; Moereels, H.; Raymaekers, L. A. Atlas Of The Three-Dimensional Structure Of Drugs; Elsevier: North-Holland, 1979; Vol. 1, Chapter 2.

New Dibenzothiadiazepine Derivatives

differences between our compound 12, tianeptine, and other antidepressants.

Experimental Procedure

Pharmacology. Male Swiss albino mice (Nossan, Milan, Italy), 20-22 g, were used. The potential antidepressant activity of compounds was evaluated by the apomorphine²³ and reserpine tests.²⁴ A preliminary "screening" on apomorphine 16 mg/kg sc (Apo 16) induced hypothermia with a high dose (400 mg/kg os) of the various compounds with temperature measurement at 0.5, 2, 4 h after administration of the product was carried out (Table II). Results are expressed for time of peak activity which was generally 0.5 h.

On subsequent evaluation, the efficacy of active compounds was quantified as the dose reducing the hypothermic response of apomorphine (ED₅₀) by 50% at time of peak activity (0.5-2)h). When the reserpine test was used, the minimal dose of compound capable of reducing significantly reserpine-induced hypothermia was determined.

In studies on physostigmine lethality, physostigmine was administered as a 0.9 mg/kg ip dose 1 h after oral administration of the compounds. Lethal effects were evaluated 24 h after this. The 50% lethal dose of compounds was evaluated for up to 2 weeks from their administration.

In all cases, each experimental group consisted of 8-20 mice.

Chemistry. Analyses indicated by the symbols of the elements were within $\pm 0.4\%$ of the theoretical value and were conducted by the Analytical Department of Menarini. Melting points were determined on a Büchi apparatus in open capillaries and are uncorrected. ¹H NMR spectra were recorded on a Varian EM-360L spectrometer with tetramethylsilane (TMS) as internal standard. IR spectra were recorded on a Perkin-Elmer FT 1710 spectrophotometer. Arylsulfonyl chlorides 1 and 1a were obtained according to known methods;^{25,26} 2-haloanilines 2 are commercially available products, only 2-bromo-5-chloroaniline was synthesized as reported.27

General Procedure for the Preparation of N-(2-Halophenyl)-2-nitrobenzenesulfonamides (3a-j). Substituted 2-nitrobenzenesulfonyl chlorides 1 (0.1 mol) in tetrahydrofuran (80 mL) was added dropwise to a solution of substituted 2haloanilines 2 (0.1 mol) in pyridine (0.15 mol) and refluxed for 2 h. After this time, solvent was removed, and the residue was washed with 10% HCl and with water, dried, and crystallized to give the following.

N-(2-bromophenyl)-2-nitrobenzenesulfonamide (3a; $R_2 = H$, $R_3 = H$) (lit.³ m. p. 147 °C), N-(2-bromophenyl)-2-nitro-4chlorobenzenesulfonamide (3b; $R_2 = 4$ -Cl, $R_3 = H$) [60%, mp (EtOH) 143-144 °C. Anal. (C₁₂H₈BrClN₂O₄S) C, H, N.], N-(2bromophenyl)-2-nitro-4-methoxybenzenesulfonamide (3c; $R_2 =$ 4-OCH₃, $R_3 = H$) [55%, mp (EtOH) 95–97 °C. Anal. (C₁₃H₁₁-BrN₂O₅S) C, H, N.], N-(2-bromophenyl)-2-nitro-4-(trifluoromethyl)benzenesulfonamide (3d; $R_2 = 4 \cdot CF_3$, $R_3 = H$) [48%, mp (EtOH) 130-131 °C. Anal. ($C_{13}H_8BrF_3N_2O_4S$) C, H, N.], N-(2,4-dichlorophenyl)-2-nitrobenzenesulfonamide $(3e; R_2 = H, R_3)$ = 4-Cl) [58%, mp (EtOH) 121-122 °C. Anal. $(C_{12}H_8Cl_2N_2O_4S)$ C, H, N.], N-(4-methyl-2-bromophenyl)-2-nitrobenzenesulfonamide (3f; $R_2 = H$, $R_3 = 4$ -CH₃) [64%, mp (EtOH) 138–139 °C. Anal. (C₁₃H₁₁BrN₂O₄S) C, H, N.], N-(5-chloro-2-bromophenyl)-2-nitrobenzenesulfonamide (3g; $R_2 = H$, $R_3 = 5$ -Cl) [74%, mp (EtOH) 128-129 °C. Anal. (C₁₂H₈BrClN₂O₄S) C, H, N.], N-(2-bromophenyl)-4-methyl-2-nitrobenzenesulfonamide (3h; R_2 = 4-CH₃, $R_3 = H$) [71%, mp (EtOH) 137-139 °C. Anal. (C₁₃- $H_{11}BrN_2O_4S)$ C, H, N.], and N-(2-bromophenyl)-2-nitro-5-chlorobenzenesulfonamide (3i; $R_2 = 5$ -Cl, $R_3 = H$) [85%, mp (EtOH) 144-145 °C. Anal. ($C_{12}H_8BrClN_2O_4S$) C, H, N.].

Synthesis of N-(2-Bromophenyl)-4-chloro-5-methyl-2amidobenzenesulfonamide (4j). 2-Amino-4-chloro-5-methylbenzenesulfonyl chloride (24 g, 0.1 mol) in tetrahydrofuran (80 mL) was added dropwise to a solution of 2-bromoaniline (17.2 g, 0.1 mol) in pyridine (15 mL) and refluxed for 2 h. After this time, solvent was removed, and the solid residue was washed with 10% HCl and with water, dried, and crystallized from EtOH to yield 30 g (80%) of 4j, mp 158-159 °C. Anal. (C₁₃H₁₂BrClN₂O₂S) C. H. N.

General Procedure for the Preparation of N-(2-Halophenyl)-2-(acetylamino)benzenesulfonamides 5a-i. Hydrogen-reduced iron powder (0.5 mol) was added portionwise to a refluxing solution of substituted 3a-i (0.1 mol) in acetic acid (300 mL). After 1 h of reflux, the hot mixture was filtered by suction. The filtrate was treated with 10 mL of acetic anhydride and was allowed to stand overnight. After dilution with water the precipitate was collected, washed with water, dried, and crystallized to give the following: N-(2-bromophenyl)-2-(acetylamino)benzenesulfonamide (5a; $R_2 = H$, $R_3 = H$) [83%, mp (EtOH) 170–171 °C. Anal. ($C_{14}H_{13}BrN_2O_3S$) C, H, N.], N-(2-bromophenyl)-2-(acetylamino)-4-chlorobenzenesulfonamide (5b; $R_2 = 4$ -Cl, $R_3 = H$) [88%, mp (EtOH) 145–147 °C. Anal. ($C_{14}H_{12}$ -BrClN₂O₃S) C, H, N.], N-(2-bromophenyl)-2-(acetylamino)-4methoxybenzenesulfonamide (5c; $R_2 = 4$ -OCH₃, $R_3 = H$) [90%, mp (EtOH) 129-130 °C. Anal. (C₁₅H₁₅BrN₂O₄S) C, H, N.], N-(2-bromophenyl)-2-(acetylamino)-4-(trifluoromethyl)benzenesulfonamide (5d; $R_2 = 4$ -CF₃, $R_3 = H$) [90%, mp (EtOH) 187–188 °C. Anal. (C₁₅H₁₂BrF₃N₂O₃S) C, H, N.], N-(2,4-dichlorophenyl)-2-(acetylamino)benzenesulfonamide (5e; $R_2 = H, R_3 =$ 4-Cl) [97%, mp (EtOH) 170-171 °C. Anal. (C₁₄H₁₂Cl₂N₂O₃S) C, H, N.], N-(4-methyl-2-bromophenyl)-2-(acetylamino)benzenesulfonamide (5f; $R_2 = H$, $R_3 = 4$ -CH₃) [95%, mp (EtOH) 157-158 °C. Anal. (C15H15BrN2O3S) C, H, N.], N-(2-bromo-5chlorophenyl)-2-(acetylamino)benzenesulfonamide (5g; $R_2 = H$, $R_3 = 5$ -Cl), [88%, mp (EtOH) 180–182 °C. Anal. (C₁₄H₁₂Br-ClN₂O₃S) C, H, N.], N-(2-bromophenyl)-4-methyl-2-(acetylamino)benzenesulfonamide (5h; $R_2 = 4$ -CH₃, $R_3 = H$) [96%, mp (EtOH) 150-151 °C. Anal. (C₁₅H₁₅BrN₂O₃S) C, H, N.], and N-(2-bromophenyl)-5-chloro-2-(acetylamino)benzenesulfonamide (5i; $R_2 = 5$ -Cl, $R_3 = H$) [93%, mp (EtOH) 186–188 °C. Anal. ($C_{14}H_{12}BrClN_2O_3S$) C, H, N.].

Synthesis of N-(2-Bromophenyl)-4-chloro-5-methyl-2-(acetylamino)benzenesulfonamide (5j). Acetic anhydride (4 mL) was added to a solution of 4j (15 g, 0.04 mol) in acetic acid (100 mL) and the mixture was kept at room temperature overnight. Dilution with water gave a precipitate that was collected, washed with water, dried, and crystallized from EtOH to yield 15 g (90%) of 5j, mp 149–150 °C. Anal. (C₁₅H₁₄BrClN₂O₃S) C, H, N.

General Procedure for the Preparation of N-(2-Halophenyl)-N-alkyl-2-(acetylamino)benzenesulfonamides 6a-l. Substituted 5a-j (0.1 mol) was added to a solution of sodium (0.1 mol) in methyl alcohol (250 mL) with stirring. After dissolving, the appropriate alkyl halides were added with stirring, and the resulting solution either was kept for 24 h at room temperature (6a-j) or was refluxed for 4 h (6k-l).

The solution was evaporated, the residue was washed with water, dried, and crystallized to give the following: N-(2bromophenyl)-N-methyl-2-(acetylamino)benzenesulfonamide (6a; $R_1 = CH_3, R_2 = H, R_3 = H$ [92%, mp (EtOH) 92–93 °C (lit.³ mp 94 °C).], N-(2-bromophenyl)-N-methyl-2-(acetylamino)-4chlorobenzenesulfonamide (**6b**; $R_1 = CH_3$, $R_2 = 4$ -Cl, $R_3 = H$) [90%, mp (EtOH) 116-117 °C. Anal. ($C_{15}H_{14}BrClN_2O_3S$) C, H, N.], N-(2-bromophenyl)-N-methyl-4-methoxy-2-(acetylamino)benzenesulfonamide (6c; $R_1 = CH_3$, $R_2 = 4$ -OCH₃, $R_3 = H$) [88%, mp (EtOH) 105-106 °C. Anal. ($C_{16}H_{17}BrN_2O_4S$) C, H, N.], N-(2-bromophenyl)-N-methyl-4-(trifluoromethyl)-2-(acetylamino)benzenesulfonamide (6d; $R_1 = CH_3$, $R_2 = 4-CF_3$, $R_3 = H$) [90%, mp (cyclohexane) 91–92 °C. Anal. ($C_{18}H_{14}BrF_3N_2O_3S$) C, H, N.], N-(2,4-dichlorophenyl)-N-methyl-2-(acetylamino)benzenesulfonamide (6e; $R_1 = CH_3$, $R_2 = H$, $R_3 = 4$ -Cl) [90%, mp (i-PrOH) 90-91 °C. Anal. (C₁₅H₁₄Cl₂N₂Ŏ₃S) C, H, N.], N-(4-methyl-2-bromophenyl)-N-methyl-2-(acetylamino)benzenesulfonamide (6f; $R_1 = CH_3$, $R_2 = H$, $R_3 = 4-CH_3$) [96%, mp (i-PrOH) 93-94 °C. Anal. (C₁₆H₁₇BrN₂O₃S) C, H, N.], N-(2-bromo-5-chlorophenyl)-N-methyl-2-(acetylamino)benzenesulfonamide (6g; $R_1 = CH_3$, $R_2 = H$, $R_3 - 5$ -Cl) [95%, mp (EtOH) 109-111 °C. Anal. (C15H14BrClN2O3S) C, H, N.], N-(2-bromo-

⁽²⁴⁾ Bourin, M.; Poncelet, M.; Chermat, R.; Simon, P. Arzneim.-Forsch/Drug Res. 1983, 33, 1173. Meerwein, H.; Dittmar, G.; Gollner, R.; Hafner, K.; Mensch,

⁽²⁵⁾ F.; Steinfort, O. Chem. Ber. 1957, 90, 841.

Bierbaum, B. A.; Traverso, J. J.; Whitehead, C. W. J. Med. (26)Chem. 1963, 6, 272.

Mahajanshetti, C. S.; Patil, V. D.; Acharya, S. P.; Nargund, K. (27)S. J. Karnatak Univ. 1961, 6, 9; Chem. Abstr. 1963, 59, 8636.

phenyl)-N-methyl-4-methyl-2-(acetylamino)benzenesulfonamide (6h; R₁ = CH₃, R₂ = 4-CH₃, R₃ = H) [98%, mp (EtOH) 115–117 °C. Anal. (C₁₈H₁₇BrN₂O₃S) C, H, N.], N-(2-bromophenyl)-Nmethyl-2-(acetylamino)-5-chlorobenzenesulfonamide (6i; R₁ = CH₃, R₂ = 5-Cl, R₃ = H) [94%, mp (EtOH) 120–121 °C. Anal. (C₁₈H₁₄BrClN₂O₃S) C, H, N.], N-(2-bromophenyl)-N-methyl-4chloro-5-methyl-2-(acetylamino)benzenesulfonamide (6j; R₁ = CH₃; R₂ = 4-Cl, 5-CH₃; R₃ = H) [84%, mp (EtOH) 148–149 °C. Anal. (C₁₆H₁₆BrClN₂SO₃) C, H, N.], N-(2-bromophenyl)-Nethyl-2-(acetylamino)benzenesulfonamide (6k; R₁ = C₂H₅, R₂ = H, R₃ = H) [70%, mp (EtOH) 92–93 °C. Anal. (C₁₈H₁₇BrN₂O₃S) C, H, N.], and N-(2-bromophenyl)-N-propyl-2-(acetylamino)benzenesulfonamide (6i; R₁ = C₃H₇, R₂ = H, R₃ = H) [76%, mp (EtOH) 87–88 °C. Anal. (C₁₇H₁₉BrN₂O₃S) C, H, N.].

General Procedure for the Preparation of 6,11-Dihydrodibenzo[c,f][1,2,5]thiadiazepine 5,5-Dioxides 7a-l. A solution of substituted 6a-l (0.1 mol) in DMF (400 mL) was treated with K₂CO₃ (13.8 g, 0.1 mol), copper powder (3 g), and CuBr (1.5 g), stirred, and heated to reflux for 8 h. After cooling, the reaction mixture was filtered and the solution diluted with water; the precipitate was collected, washed with water, dried, and crystallized to give products as outlined in Table I.

6-Methyl-6,11-dihydro-11-(chloroacetyl)dibenzo[c, f]-[1,2,5]thiadiazepine 5,5-Dioxide (9a). 7a (15 g, 0.057 mol) in chloroacetyl chloride (100 mL) was refluxed for 2 h. The cooled mixture was poured on ice and stirred until decomposition of the acid chloride and solidification of the product. The solid was collected, washed with water, dried, and crystallized from ethyl acetate to yield 15.3 g (80%) of 9a: mp 141–143 °C; IR (Nujol) 1690 cm⁻¹; ¹H NMR (CDCl₃) δ 3.3 (s, 3 H, CH₃), 4.05 (s, 2 H, CH₂), 7.2–8.2 (m, 8 H, arom). Anal. (C₁₅H₁₃ClN₂O₃S) C, H, N.

Similar reactions with the appropriate 6,11-dihydrodibenzo-[c,f][1,2,5]thiadiazepine 5,5-dioxides gave the products 9b-m shown in Table I.

6-Methyl-6,11-dihydro-11-[(N,N-dimethylamino)acetyl]dibenzo[c,f][1,2,5]thiadiazepine 5,5-Dioxide (12). A solution of 9a (7 g, 0.0206 mol) in acetone (70 mL) was treated with dimethylamine (40 wt% solution in water, 7 mL) and stirred at room temperature. After 2 days the reaction mixture was concentrated. The residue was dissolved in HCl 10% and the insoluble part removed. After alkalinization with Na₂CO₃ of the watery solution, the precipitate was collected, washed with water, dried, and crystallized from EtOH to yield 5 g (70%) of 12: mp 179-181 °C; IR (Nujol) 1689 cm⁻¹; ¹H NMR (CDCl₃) δ 2.3 (s, 6 H, N(CH₃)₂), 3.05 (s, 2 H, CH₂), 3.3 (s, 3 H, CH₃), 7.1-8 (m, 8 H, arom). Anal. (C₁₇H₁₉N₃O₃S) C, H, N.

With a similar procedure starting from the appropriate compounds 9a-m and alkylamines, the products 17, 18, 21, 22, 24, 25, and 29-38 shown in Table II were obtained.

2-Chloro-3,6-dimethyl-6,11-dihydro-11-[(4-methylpiperazin-1-yl)acetyl]dibenzo[c,f][1,2,5]thiadiazepine 5,5-Dioxide (13). A solution of 9j (5 g, 0.013 mol) and of *N*methylpiperazine (3 mL, 0.02 mol) in acetone (50 mL) was refluxed for 2 h. The mixture was then evaporated, the residue was dissolved in HCl 10%, and the insoluble part was removed. The watery solution was alkalinized with Na₂CO₃, the precipitate collected, washed with water, dried, and crystallized from 2-PrOH to yield 4.3 g (74%) of 13: mp 156-158 °C; IR (Nujol) 1693 cm⁻¹; ¹H NMR (DMSO- d_6) δ 1.8-2.4 (m, 14 H, 2 CH₃ + piperaz), 2.8-3.3 (m, 5 H, CH₂ + CH₃), 7.2-7.9 (m, 6 H, arom). Anal. (C₂₁H₂₅-ClN₄O₃S) C, H, N.

A similar procedure starting from the appropriate compounds 9a-m and amines gave the products 14-16, 19, 20, 23, and 26-28 shown in Table II.

6-Methyl-6,11-dihydro-11-carbamoyldibenzo[c,f][1,2,5]thiadiazepine 5,5-Dioxide (10). NaH in oil (about 80%, 0.9 g) was added to a stirred solution of 7a (7 g, 0.027 mol) in dioxane (200 mL) and kept at 80 °C for 30 min. After cooling in a ice-bath, trichloromethyl chloroformate (5.4 g, 0.027 mol) was added and after 1 h the mixture was saturated with gaseous NH₃. The mixture was filtered, the solvent was removed and the residue

Table V. Crystal and Refinement Data for 12

mol formula	C ₁₇ H ₁₉ N ₃ O ₂ S				
mol weight	329.42				
a. Å	8.829 (3)				
b. Å	8.297 (8)				
c. Å	23.655 (8)				
β , deg	92.74 (3)				
V. Å ³	1712.0 (4)				
Z	4				
space group	$P2_1/c$				
d _{outer} g·cm ⁻³	1.28				
radiation	graphite monochromated				
	Mo-K α (λ + 0.7107 Å)				
temp, °C	25				
$m. \mathrm{cm}^{-1}$	1.66				
Rª	0.077				
AD - SHEL IEH/SIEL					

 ${}^{a}R = \sum ||F_{o}| - |F_{c}|| / \sum |F_{o}|.$

washed with water, dried, and crystallized from EtOH to yield 4.9 g (60%) of 10: mp 240-242 °C; IR (Nujol) 1685 cm⁻¹; ¹H NMR (DMSO- d_{6}) δ 3.3 (s, 3 H, CH₃), 6.2 (s, 2 H, NH₂), 7.1-7.8 (m, 8 H, arom). Anal. (C₁₄H₁₃N₃O₃S) C, H, N.

By the same procedure and starting from 7a with gaseous $HN(CH_3)_2$, 11 as shown in Table II was obtained.

6-Methyl-6,11-dihydro-11-(aminoacetyl)dibenzo[c,f]-[1,2,5]thiadiazepine 5,5-Dioxide Hydrochloride (39). mixture of 9a (6.3 g, 0.019 mol), toluene (10 mL), and NaN₃ (3 g, 0.019 mol) in water (12 mL) with Aliquat 356 (0.8 g, 0.02 mol) was stirred for 16 h. The mixture was filtered, the insoluble solid was collected, washed with water and dried: the crude azido derivative was obtained. It was then suspended in methanol (400 mL), treated with 10% palladium-charcoal catalyst (1 g) and hydrogenated at atmospheric pressure and room temperature until uptake of hydrogen ceased (8 h). After filtration to remove the catalyst, the solution was evaporated under vacuum. The residue was dissolved in chloroform and saturated with gaseous HCl. The precipitate was then collected, dried, and crystallized from 2-PrOH to yield 3.1 g (46%) of 39: mp 242-244 °C dec; IR (Nujol) 1693 cm^{-1} ; ¹H NMR (DMSO-d₆) 3-4.1 (m, 5 H, CH₃ + CH₂), 7.3-8.1 (m, 8 H, arom). Anal. $(C_{15}H_{15}N_3O_3S \cdot HCl)$ C, H, N.

X-ray Crystal Structure Determination. A single crystal of 12 with approximate dimensions $0.3 \times 0.2 \times 0.1$ mm was mounted on a Enraf-Nonius CAD4 X-ray diffractometer. A summary of the crystallographic data is reported in Table V. Unit-cell parameters were determined from angular settings of 25 carefully centered reflections. Intensities were corrected for Lorentz and polarization effects. The intensities of three standard reflections were monitored periodically for stability control during data collection. A total of 2470 reflections were collected in the range 5° < 2 θ < 45°. A total of 1126 reflections with $I > 3\sigma(I)$ were used in the structure determination. The structure was solved by direct methods of SHELX76 that show all the non-hydrogen atoms.²⁸ Refinement was performed by means of the full-matrix least-squares methods of SHELX76. Hydrogen atoms were introduced in calculated positions, and their parameters were refined successively. Isotropic thermal parameters were used for carbon and hydrogen atoms, while sulfur, oxygen, and nitrogen atoms were refined anisotropically.

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Supplementary Material Available: Tables listing positional parameters for hydrogen and non-hydrogen atoms, atomic thermal parameters, bond distances, bond angles, and possible hydrogen bonds (6 pages). Ordering information is given on any current masthead page.

⁽²⁸⁾ Sheldrick, G. M. SHELX76, Program for Crystal Structure Determination; University of Cambridge: Cambridge, U.K. 1976.