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Synthesis and Pharmacological Activity of 5-Substituted 2-(*N,N*-Dialkylaminoethyl)amino- and 2-*N*-Methylpiperazinyl-1,3,4-thiadiazoles

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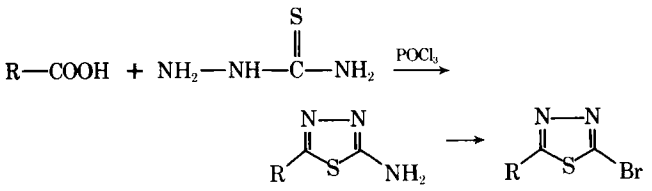
Abstract □ 5-Substituted 2-amino-1,3,4-thiadiazoles were transformed to their corresponding 2-bromo derivatives. The reaction of the 5-substituted 2-bromo-1,3,4-thiadiazoles with *N,N*-dialkylaminoethylamines or *N*-methylpiperazine afforded the corresponding amino-1,3,4-thiadiazole derivatives. All prepared compounds displayed antihistaminic, anticholinergic, and norepinephrine-potentiating activities.

Keyphrases □ 1,3,4-Thiadiazoles, 5-substituted 2-(*N,N*-dialkylaminoethyl)amino and 2-*N*-methylpiperazinyl—synthesis, antihistaminic, anticholinergic, and norepinephrine-potentiating activities □ 2-(*N,N*-Dialkylaminoethyl)amino-1,3,4-thiadiazoles, 5-substituted—synthesis and pharmacological activity □ 2-*N*-Methylpiperazinyl-1,3,4-thiadiazoles, 5-substituted—synthesis and pharmacological activity □ Antihistaminic, anticholinergic, and norepinephrine-potentiating activities—synthesis and screening of 5-substituted 2-(*N,N*-dialkylaminoethyl)amino- and 2-*N*-methylpiperazinyl-1,3,4-thiadiazoles

In continuing studies on the chemistry and pharmacological activity of 1,3,4-thiadiazoles and their derivatives, it was of interest to introduce the =N—CH_2CH_2—N= moiety, the important group in known compounds with antihistaminic activity, to the 1,3,4-thiadiazole ring system. A previously reported method was used for the preparation of 2-amino-5-substituted-1,3,4-thiadiazoles (1, 2); the 2-amino compounds were then transformed to their corresponding 2-bromo compounds by a modified Sandmeyer reaction (3) (Scheme I).

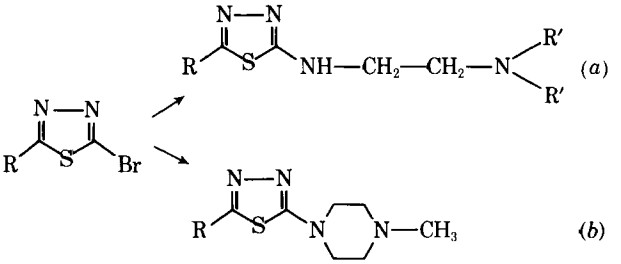


Scheme I

The 2-bromo-5-substituted-1,3,4-thiadiazoles thus obtained were subjected to a nucleophilic substitution reaction with *N*-methylpiperazine or asymmetrical dialkylaminoethylamine (Scheme II).

EXPERIMENTAL

Synthesis of 5-Substituted 2-*N*-Methylpiperazinyl- and 2-*N,N*-Dialkylaminoethylamino-1,3,4-thiadiazole Hydrochlorides—5-Substituted 2-bromo-1,3,4-thiadiazole (0.01 mole) and 2 *M* portions of *N*-methylpiperazine or asymmetric dialkylethylenediamine were refluxed for 8 hr in 40 ml of dry benzene. After cooling, the solid hydrobromide of the starting amine was separated by



Scheme II

1*a*: R = *o*-$CH_3C_6H_4$, R′ = CH_3
2*a*: R = *m*-$CH_3C_6H_4$, R′ = CH_3
3*a*: R = *p*-$CH_3C_6H_4$, R′ = CH_3
4*a*: R = *m*-$CH_3C_6H_4$, R′ = C_2H_5
5*a*: R = *p*-$CH_3OC_6H_4$, R′ = CH_3
6*a*: R = *m*-$NO_2C_6H_4$, R′ = CH_3
7*a*: R = *m*-$NO_2C_6H_4$, R′ = C_2H_5
8*a*: R = *p*-$NO_2C_6H_4$, R′ = CH_3
9*a*: R = *p*-$NO_2C_6H_4$, R′ = C_2H_5

1*b*: R = CH_3
2*b*: R = C_2H_5
3*b*: R = CF_3
4*b*: R = C_6H_5
5*b*: R = *o*-$CH_3C_6H_4$
6*b*: R = *m*-$CH_3C_6H_4$
7*b*: R = *p*-$CH_3C_6H_4$
8*b*: R = *m*-$CH_3OC_6H_4$
9*b*: R = *p*-$CH_3OC_6H_4$
10*b*: R = *p*-FC_6H_4
11*b*: R = *o*-ClC_6H_4
12*b*: R = *m*-ClC_6H_4
13*b*: R = *p*-ClC_6H_4
14*b*: R = *m*-BrC_6H_4
15*b*: R = *p*-BrC_6H_4
16*b*: R = *m*-$NO_2C_6H_4$
17*b*: R = *p*-$NO_2C_6H_4$

Table I—5-Substituted 2-(*N*,*N*-Dialkylaminoethyl)amino-1,3,4-thiadiazoles

Compound	Molecular Formula	Molecular Weight	Melting Point	Yield, %	Analysis, % Calc.	Found
1*a*	$C_{13}H_{18}N_4S$	262	173°	22	C 59.54 H 6.87	59.62 6.80
2*a*	$C_{13}H_{18}N_4S$	262	198°	50	C 59.54 H 6.87	59.48 6.89
3*a*	$C_{13}H_{18}N_4S$	262	218°	47	C 59.54 H 6.87	59.46 6.86
4*a*	$C_{15}H_{22}N_4S$	290	171°	6	C 62.06 H 7.58	61.93 7.52
5*a*	$C_{13}H_{18}N_4OS$	278	152°	10	C 56.11 H 6.47	56.06 6.53
6*a*	$C_{12}H_{15}N_5O_2S$	293	234°	9	C 49.14 H 5.11	49.22 5.05
7*a*	$C_{14}H_{19}N_5O_2S$	321	201°	53	C 52.33 H 5.91	52.38 5.94
8*a*	$C_{12}H_{15}N_5O_2S$	293	257°	26	C 49.14 H 5.11	49.10 5.07
9*a*	$C_{14}H_{19}N_5O_2S$	321	273°	49	C 52.33 H 5.91	52.30 6.08

Table II—5-Substituted 2-*N*-Methylpiperazinyl-1,3,4-thiadiazoles

Compound	Molecular Formula	Molecular Weight	Melting Point	Yield, %	Analysis, % Calc.	Found
1*b*	$C_8H_{14}N_4S$	198	250°	56	C 48.48 H 7.07	48.59 7.02
2*b*	$C_9H_{16}N_4S$	212	149°	39	C 50.92 H 7.55	50.87 7.50
3*b*	$C_8H_{11}F_3N_4S$	252	234°	57	C 38.10 H 4.37	38.11 4.43
4*b*	$C_{13}H_{16}N_4S$	260	276°	80	C 60.00 H 6.15	60.12 6.21
5*b*	$C_{14}H_{18}N_4S$	274	220°	87	C 61.31 H 6.57	61.28 6.50
6*b*	$C_{14}H_{18}N_4S$	274	283°	71	C 61.31 H 6.57	61.30 6.64
7*b*	$C_{14}H_{18}N_4S$	274	292°	69	C 61.31 H 6.57	61.39 6.63
8*b*	$C_{14}H_{18}N_4OS$	290	217°	58	C 57.93 H 6.21	57.86 6.29
9*b*	$C_{14}H_{18}N_4OS$	290	233°	68	C 57.93 H 6.21	57.92 6.12
10*b*	$C_{13}H_{15}FN_4S$	278	283°	38	C 56.12 H 5.40	56.20 5.44
11*b*	$C_{13}H_{15}ClN_4S$	294.5	231°	94	C 52.97 H 5.09	52.90 5.01
12*b*	$C_{13}H_{15}ClN_4S$	294.5	296°	82	C 52.97 H 5.09	52.98 5.16
13*b*	$C_{13}H_{15}ClN_4S$	294.5	291°	64	C 52.97 H 5.09	52.89 5.08
14*b*	$C_{13}H_{15}BrN_4S$	339	304°	56	C 46.03 H 4.42	46.09 4.36
15*b*	$C_{13}H_{15}BrN_4S$	339	277°	49	C 46.03 H 4.42	46.13 4.50
16*b*	$C_{13}H_{15}N_5O_2S$	305	265°	60	C 51.15 H 4.92	51.18 4.83
17*b*	$C_{13}H_{15}N_5O_2S$	305	246°	20	C 51.15 H 4.92	51.04 4.98

filtration and the benzene solution was extracted with 5% hydrochloric acid. The aqueous layer was evaporated under reduced pressure, and the solid residue was recrystallized from absolute ethanol.

The free base of 5-phenyl-2-*N*-methylpiperazinyl-1,3,4-thiadiazole was prepared as follows. The hydrochloride was dissolved in water and made basic with concentrated sodium hydroxide, and the solid was separated and recrystallized from ethyl acetate, mp 112°.

Physical properties of the synthesized compounds are found in Tables I and II.

Antihistaminic and Anticholinergic Activities—Isolated guinea pig ileum was prepared according to the method of Magnus (4) and suspended in a 10-ml bath filled with Tyrode solution, which was aerated at 30°. The isotonic contractions were magnified sixfold and recorded with a frontal writing lever on smoked drum. The pA_2 values were determined by the method of Schild (5).

Table III—Antihistaminic, Anticholinergic, and Norepinephrine-Potentiating Effects of 5-Substituted 2-(*N,N*-Dialkylaminoethyl)amino- and 2-*N*-Methylpiperazinyl-1,3,4-thiadiazoles[a]

Compound	pA_2 Values: Antihistaminic	pA_2 Values: Anticholinergic	Increase of Maximum Contraction, %
1*a*	4.55 ± 0.26 (4)	4.17 ± 0.19 (4)	—
2*a*	4.81 ± 0.5 (4)	4.72 ± 0.06 (4)	—
3*a*	4.80 ± 0.08 (4)	4.61 ± 0.11 (4)	—
4*a*	4.96 ± 0.04 (4)	5.01 ± 0.07 (4)	100 ± 19.14
5*a*	4.89 ± 0.09 (5)	4.84 ± 0.02 (4)	—
6*a*	4.75 ± 0.11 (4)	4.80 ± 0.32 (4)	—
7*a*	5.37 ± 0.05 (4)	5.06 ± 0.06 (4)	33.87 ± 2.78
8*a*	5.09 ± 0.07 (4)	4.89 ± 0.11 (4)	22.05 ± 1.76
9*a*	5.41 ± 0.12 (4)	5.34 ± 0.08 (4)	120.25 ± 13.44
1*b*	3.75 ± 0.10 (4)	3.38 ± 0.07 (4)	—
2*b*	3.91 ± 0.09 (4)	3.96 ± 0.16 (4)	—
3*b*	4.31 ± 0.05 (3)	4.43 ± 0.22 (4)	17.95 ± 21.93
4*b*	3.87 ± 0.12 (3)	3.68 ± 0.07 (4)	—
5*b*	4.01 ± 0.13 (4)	4.02 ± 0.05 (4)	—
6*b*	3.96 ± 0.10 (4)	4.04 ± 0.06 (4)	—
7*b*	4.22 ± 0.13 (4)	4.26 ± 0.14 (4)	—
8*b*	4.34 ± 0.02 (4)	4.37 ± 0.03 (4)	—
9*b*	3.72 ± 0.11 (4)	3.95 ± 0.11 (4)	—
10*b*	4.35 ± 0.12 (4)	4.21 ± 0.01 (4)	—
11*b*	4.03 ± 0.08 (4)	4.12 ± 0.12 (4)	—
12*b*	4.34 ± 0.11 (4)	4.33 ± 0.13 (4)	—
13*b*	4.50 ± 0.05 (4)	4.32 ± 0.07 (4)	34.92 ± 8.49
14*b*	4.64 ± 0.09 (4)	4.67 ± 0.09 (4)	39.97 ± 5.25
15*b*	4.43 ± 0.07 (4)	4.37 ± 0.06 (4)	—
16*b*	4.32 ± 0.10 (5)	4.34 ± 0.08 (4)	—
17*b*	4.94 ± 0.26 (4)	4.60 ± 0.11 (4)	24.07 ± 5.94
Atropine	—	9.84 ± 0.17 (4)	—
Diphenhydramine	9.74 ± 0.42 (4)	—	—
Cocaine	—	—	28.95 ± 10.83

[a] Values are expressed as mean ±*SE*. Numbers in parentheses indicate the number of experiments. When studying the norepinephrine-potentiating effect, Compounds 7*a*, 8*a*, and 9*a* were used in a concentration of 1×10^{-6} *M* and the other compounds were used in a concentration of 1×10^{-5} *M*.

Histamine and acetylcholine were used as agonists, and diphenhydramine and atropine were tested for comparison.

Norepinephrine-Potentiating Effect—Preliminary experiments revealed that some of these compounds potentiated the effect of norepinephrine on vas deferens; therefore, Compounds 4*a*, 7*a*, 8*a*, 9*a*, 3*b*, 13*b*, 14*b*, and 17*b* were tested on isolated rat vas deferens. The tissue was mounted in the bath under 1 g of tension. Isometric contractions were amplified and recorded[1] through a photosensitive myograph transducer. The test compounds were added 3 min before norepinephrine administration, and results were compared with contraction induced by norepinephrine in the absence of the compounds.

LD_{50} Determination—The toxicity of the sufficiently available compounds was determined in ordinary mice by the moving average method (6). The compounds were injected intraperitoneally; six animals were used for each dose.

RESULTS AND DISCUSSION

The potency of antihistaminic and anticholinergic activities is given in Table III and compared with diphenhydramine and atropine. The pA_2 values show that dialkylaminoethylamine derivatives possessed approximately three to four times more antihistaminic and anticholinergic potency than *N*-methylpiperazine derivatives.

Nitrophenyl, bromophenyl, and methoxyphenyl as well as trifluoromethyl compounds were found to be more active. Compounds substituted in the *para*-position were more active than the corresponding *ortho*- and *meta*-substituted derivatives. 5-Trifluoromethyl-2-*N*-methylpiperazinyl-1,3,4-thiadiazole was much more active than the corresponding 5-methyl, 5-ethyl, and 5-phenyl derivatives.

In the ethylenediamine series, compounds having a diethyl group were two to three times more active as compared with dimethyl derivatives, probably due to an increase in hydrophobicity.

It is also suggested that the lower activity in the piperazine series is due to the large size of the piperazine moiety of the molecule.

The potentiation of the effect of norepinephrine on α-receptors of vas deferens by these compounds, particularly 9*a*, is remarkable as compared with that of cocaine. This effect was significantly greater with the ethylenediamine series as compared with the piperazine series (Table III).

The LD_{50}'s of Compounds 2*b*, 3*b*, 4*b*, and 7*a* were 124.4 (107.4–144), 51.7 (44.2–60.5), 261.7 (222.7–307.5), and 148.2 (120.5–182.4) mg/kg, respectively. The trifluoromethyl group increased the toxicity of the compounds.

The animals showed hyperexcitability and tonic convulsions before death.

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[1] E. & M. physiograph.