imidoethane Iodide (7). To 7.3 g (1.98 mmoles) of **5** in 150 ml of abs EtOH was added gradually MeI (3.76 g, 26.5 mmoles) and the mixt was refluxed for 1 hr. On standing, 7 pptd; some more 7 pptd on addn of dry Et_2O. The light-sensitive salt was filtered, washed (Et_2O), and dried at 0°, yield 9.2 g (91.1%), mp 186–187°. *Anal.* ($C_{22}H_{27}IN_2O_4$) C, H, N; *m/e* 368 ($M^+ - CH_3I$).

The homologous salt **(8)** prepd from **6** was obtd in 99% yield, mp 152–153°. *Anal.* ($C_{23}H_{29}IN_2O_4$) C, H, N.

Hydrazinolysis of Methiodides 7 and 8. To a suspension of 8 or 7 (2.4–2.55 g, 4.5–5 mmoles) in 25 ml of 95% EtOH was added 0.7–0.75 g (*ca.* 14.5 mmoles) of 64% hydrazine hydrate. The mixt turned pale yellow and the solid went into soln on heating. After 2 hr of reflux and cooling overnight, a white ppt had formed. HCl (37%) was added dropwise to Congo Red, and the yellowish ppt was filtered off and washed with EtOH and then H_2O, and the filtrate was evapd. Recrystn of the pale yellow residue from EtOH and from hexane gave 1.28 g (61.5%) of **3-methoxy-4-trimethylammoniumethoxyphenethylamine·HCl·I⁻ (9)**, mp 181–182° dec [*Anal.* ($C_{14}H_{26}ClIN_2O_2$) C, H], and **1-(3-methoxy-4-trimethylammoniumethoxyphenyl)-2-aminopropane·HCl·I⁻ (10)** (1.4 g, 71%), mp 177–179° dec [*Anal.* ($C_{15}H_{28}ClIN_2O_2$) C, H, N], respectively.

Hydrazinolysis of 5 and 6. To an iced aqueous soln of salts **5** (or **6**) (0.01 mole) was added NaOH (0.01 mole) and the liberated amine was extd with Et_2O (3 × 50 ml). The solvent was evapd, and the residue dissolved in 25 ml of EtOH and a 10% excess of 64% hydrazine hydrate. The warm mixt was refluxed for 45 min, then 6 *N* HCl (2 ml) was added dropwise. Phthalhydrazide was filtered off and washed (EtOH, H_2O), the filtrate was concd, and a white ppt was filtered off. The yellow residue from the evapd filtrate was recrystd from abs EtOH: **4-dimethylaminoethoxy-3-methoxyphenethylamine·2HCl (11)**, mp 198–200° dec, yield 36% [*Anal.* ($C_{13}H_{24}Cl_2N_2O_2·H_2O$) C, H, N]; **1-(4-dimethylaminoethoxy-3-methoxyphenyl)-2-aminopropane·2HCl (12)**, mp 209–211°, yield 54% [*Anal.* ($C_{14}H_{26}Cl_2N_2O_2$) C, H, N; *m/e* 252 (M^+)].

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1,4-Disubstituted Piperazines. 3. Piperazinylbenzothiazoles†

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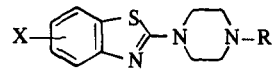
In the course of synthesis of 1,4-disubstituted piperazines,[1] 4-(2-benzothiazolyl)-*N,N*-diethyl-1-piperazinecarboxamide (**2**) was prepared and appeared to exhibit activity against coccidiosis in chickens. Since 2-(1-piperazinyl)-benzothiazole was new to the literature, the synthesis and biological studies of this parent and its derivatives **I**, reported in this paper, were undertaken. Retesting of **2**, however, failed to sustain coccidiostatic activity; nor was this activity shown by any of the type I compounds. Of interest, though, was the antifungal action and CNS effects shown by some of these piperazinylbenzothiazoles.

Biological Data.‡ Compds **1**, **5**, and **6** were marginal psychomotor stimulants in mice at 300 mg/kg po. Compd **1** also showed antihypertensive activity in rats (approx ED_{50} = 6 mg/kg sc). Compds **8** and **14** produced decreased locomotor activity in mice at 16 mg/kg po, and 64 mg/kg po, respectively. Mice were hyperactive at 256 mg/kg po with **20**, **21**, **22**, and **23**. They showed ataxia at 256 mg/kg po with **24**. In spot tests against *Trichophton mentagrophytes*, *Asperigillus niger*, and *Candida albicans*, **21**, **22**, **23**, and **24** were active. Compd **9** showed marginal *in vitro* activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Proteus vulgaris*, but was inactive against staphylococcal infections in mice. Many of these compounds were also tested for possible anthelmintic, amebi-



I

asis, antimalarial, schistosomiasis, antiviral, and antiinflammatory activities.

Experimental Section §

All microanalyses were performed at the Sterling-Winthrop Research Institute. The chemicals were either purchased from Eastman, K and K, or Aldrich, including 1-methylpiperazine and 2-(1-piperazinyl)ethanol. The following monosubstituted piperazines were prepd by literature methods: 1-(*N,N*-diethylcarbamoyl)piperazine,[2] 1-formylpiperazine,[3] 1-diphenylmethylpiperazine,[4] 1-(2-*N,N*-dimethylaminoethyl)piperazine,[5] 1-benzylpiperazine,[6] and 1-*p*-chlorophenylpiperazine.[7]

Also prepd as intermediates were: 2-bromo-4-chlorobenzothiazole,[8] 2-chloro-6-methoxybenzothiazole,[9] 2-chloro-6-nitrobenzothiazole,[10] and 1-chloroacetyl-3-methylurea.[11] 2-Chloro-6-ethoxybenzothiazole was prepd according to the procedure used in making 2-chloro-6-methoxybenzothiazole, but was not analyzed: mp 63–67° from hexane.

1,4-Disubstituted Piperazines (Table I). Procedure A. One equiv of the alkyl halide was slowly added to a vigorously agitated mixt of 2 equiv of piperazine in 80% alcohol plus excess $NaHCO_3$ heated at reflux. After filtration, the solvent was removed under reduced pressure. Addn of concd HCl resulted in pptn of the corresponding salt for **1**. For **15**, in addn to many other compds here described, dil HCl dissolved the residue, which was then washed with Et_2O or EtOAc and repptd by addn of NaOH. The products were recrystd from the solvents shown in Table I.

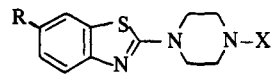
Procedure B. Two equiv of the appropriate monosubstituted piperazine was used to 1 equiv of the alkyl halide in PhH.

Procedure C. A 10% molar excess of the appropriate alkyl halide plus 2-(1-piperazinyl)benzothiazole·HCl in an excess of $NaHCO_3$ and EtOH–H_2O represented the reaction mixt.

Procedure D. Two equiv of the appropriate monosubstituted piperazine to 1 equiv of the alkyl halide in EtOH was used.

Procedure E. A 10% molar excess of the alkyl halide to the appropriate monosubstituted piperazine in excess $NaHCO_3$ plus EtOH–H_2O was used.

Procedure F. Here the mixt consisted of an EtOH soln of a 20% excess of the corresponding C=O compd plus 2-(4-amino-1-piperazinyl)benzothiazole.#



II

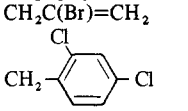
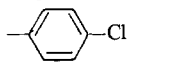
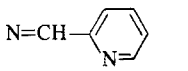
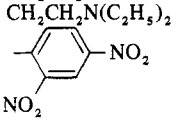
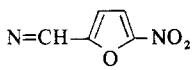
†The author wishes to acknowledge with gratitude the support of this work by the Sterling-Winthrop Research Institute, Rensselaer, N. Y.

‡The author wishes to extend his thanks to the Biological Division of Sterling-Winthrop Research Institute for conducting these studies.

§Where analyses are indicated only by symbols of the elements or functions, analytical results obtained were within ±0.4% of the theoretical values.

#This compd was prepd impure from **9** according to Conroy's[12] method of reduction of 1-(*p*-chlorophenyl)-4-nitrosopiperazine; mp 78–85° from petr ether (90–120°), followed by washing with ether.

Table I. 1,4-Disubstituted Piperazines (II)

No.	R	X	Yield, %	Mp,[a] °C	Procedure[b]	Reaction[c] time, hr	Recrystn[d] solvent	Formula	Analyses
1	H	H(HCl)	75	290 dec	A	8	A	$C_{11}H_{13}N_3S \cdot HCl$	Cl, S
2	H	$CON(C_2H_5)$	54	86–87	B	0.5 (60°)	B	$C_{16}H_{22}N_4OS$	N, S
3	H	CH_3	58	89–90	B	48 (room temp)	B	$C_{12}H_{15}N_3S$	N, S
4	H	CHO	83	142–143	B	1 (50°)	S + C	$C_{12}H_{13}N_3OS$	N, S
5	H	$CH_2C_6H_5$	92	134–135	C	4	B + C	$C_{18}H_{19}N_3S$	N, S
6	H	$CH_2C(Br)=CH_2$	89	140–141	C	3	B	$C_{14}H_{16}BrN_3S$	Br, N, S
7			47	136–137	C	3	E (first), N (second)	$C_{18}H_{17}Cl_2N_3S$	Cl, N, S
8	H	$(CH_2)_4CH_3$	60	89–89.5	C	1.8	F	$C_{16}H_{23}N_3S$	N, S
9	H	NO	68	129–130	*e*		G	$C_{11}H_{12}N_4OS$	N, S
10	H	$CH(C_6H_5)_2$	57	166.5–167.5	C	1.5	H	$C_{24}H_{23}N_3S$	N, S
11	H	CH_2COOH	54	263 dec	C	1.8 (room temp)	I	$C_{13}H_{15}N_3O_2S$	N, S
12	O_2N	H(HCl)	26	250 dec	C	2 (room temp)	J	$C_{11}H_{12}N_4O_2S \cdot HCl$	Cl, S
13	O_2N	$CH_2CH_2N(C_2H_5)_2 \cdot HCl$	54	248–250 dec	E	5 (room temp)	K	$C_{17}H_{25}N_5O_2S \cdot HCl$	Cl, N
14	CH_3O	CH_3	60	102.5–103.5	D	9	L	$C_{13}H_{17}N_3OS$	N, S
15	CH_3O	H	71	152–153	A	2.5	N + C	$C_{12}H_{15}N_3OS$	N, S
16	H	$N=C(CH_3)_2$	20	122–124	F	1	F (first), N (second)	$C_{14}H_{18}N_4S$	N, S
17	CH_3O	$CH_2C_6H_5$	60	111–112	E	10	L	$C_{19}H_{21}N_3OS$	N, S
18	H	$CH_2CONHCONHCH_3$	83	205–207	C	1	O	$C_{15}H_{19}N_5O_2S$	N, S
19	H		70	208	E	1.5	E + T (1:3)	$C_{17}H_{16}ClN_3S$	N, S
20	H		65	165–166	F	1	N + H (1:1)	$C_{17}H_{17}N_5S$	N, S
21	H	$CH_2CH_2N(C_2H_5)_2$	58	54.5–55	E	1.8	P	$C_{17}H_{26}N_4S$	N, S
22[f]	H	CH_3	82	80–81	D	9	L (first), R (second)	$C_{12}H_{14}ClN_3S$	N, S
23[f]	H	CH_2CH_2OH	69	107.5–108.5	E	8.5	S + N (1:4)	$C_{13}H_{16}ClN_3OS$	N, S
24	OC_2H_5	$CH_2CH_2N(C_2H_5)_2$	49	52–52.5	E	9.2	P	$C_{19}H_{30}N_4OS$	N, S
25	H		83	210–213	C	2 (room temp)	T	$C_{17}H_{15}N_5O_4S$	N, S
26	H	 [g]	71	201–202	F	1.3	U	$C_{16}H_{15}N_5O_3S$	N, S
27	H	$COOCH_2CH_2CH_3$	84	88–89	C	*h*	N	$C_{15}H_{19}N_3O_2S$	N, S

[a] Melting points (uncorr) were taken on a Fisher-Johns block. [b] These procedures are described in the Experimental Section. [c] Unless otherwise specified, the reactions were carried out at reflux temps. [d] A, 92% O in water; B, petr ether (65–110°); C, CCl_4; E, acetone; F, O plus H_2O; G, O first, then triturated and washed with Et_2O; H, EtOAc; I, AcOH–MeOH; J, first O, second H_2O; K, abs O; L, petr ether (60–90°); N, petr ether (90–120°); O, EtOH; P, hexane; R, petr ether (30–60°); S, benzene; T, dioxane; U, not recrystd: washed with O then ether. [e] Prepd according to a lit. method for making 1-(*p*-chlorophenyl)-4-nitrosopiperazine.[12] [f] Also bears Cl at the 4 position of the benzothiazole ring. [g] Prepd by acid treatment of 5-nitrofurfural diacetate followed by ether extn of the liberated aldehyde. [h] Heated to 60° for 5 min and set to stand overnight at room temp.

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Synthesis of 1,2,4-Triazoles as Potential Hypoglycemic Agents

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Impetus for a study of triazoles was provided by a report that certain 4-alkyl-5-aryl-4*H*-1,2,4-triazole-3-thiols produced hypoglycemia in normal and alloxan-diabetic rats. The potency of these compounds was comparable to that of N^1-(*p*-tolylsulfonamido)-N^3-(*n*-butyl)urea (tolbutamide) while their duration of action was greater.[1,2] Consequently,