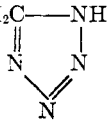
TABLE I

THIO- AND SULFONYLMETHYLTETRAZOLES



No.	R	X	Mp, °C	Crystn solvent	Formula[e]	Apparent pK_a
1	CF_3	S	99.5–100.5	*a*	$C_4H_5F_3N_4S$	4.9
2	CF_3	SO_2	195–196	*a*	$C_4H_5F_3N_4O_2S$	
3	$(CH_3)_2CH$	S	109–110	*a*	$C_5H_{10}N_4S$	5.4
4	$(CH_3)_2CH$	SO_2	155.5–156.5	*b*	$C_5H_{10}N_4O_2S$	4.0
5	3-Thienyl	S	129–130	*a*	$C_6H_6N_4S_2$	5.3
6	3-Thienyl	SO_2	160 dec	*a*	$C_6H_6N_4O_2S_2$	4.2
7	*p*-ClC_6H_4	S	159–160	*a*	$C_8H_7ClN_4S$	5.1
8	*p*-ClC_6H_4	SO_2	225 dec	*c*	$C_8H_7ClN_4O_2S$	4.0
9	*p*-$ClC_6H_4CH_2$	S	103–104	*a*	$C_9H_9ClN_4S$	5.3
10	*p*-$ClC_6H_4CH_2$	SO_2	234 dec	*d*	$C_9H_9ClN_4O_2S$	4.0
11	*p*-$CH_3C_6H_4$	S	142–143	*a*	$C_9H_{10}N_4S$	5.3
12	*p*-$CH_3C_6H_4$	SO_2	211 dec	*c*	$C_9H_{10}N_4O_2S$	4.2

[a] Et_2O. [b] EtOAc. [c] H_2O. [d] Me_2CO. [e] All compounds were analyzed for C, H, N, and neut equiv.

TABLE II

THIOACETONITRILES

$RSCH_2CN$

R	Mp or bp (mm), °C	Formula[c]
$(CH_3)_2CH$	88–90 (23)	C_5H_9NS
3-thienyl	96 (0.1)	$C_6H_5NS_2$
p-ClC_6H_4[a]	84–85	C_8H_6ClNS
p-$ClC_9H_4CH_2$	109 (0.1)	C_9H_8ClNS
p-$CH_3C_6H_4$[b]	41–42	C_9H_9NS

[a] E. A. Falco, B. Roth, and G. H. Hitchings, *J. Org. Chem.*, **26**, 1143 (1961). [b] J. M. van der Zanden, J. Nieuwenhuis, and H. J. T. Bos, *Rec. Trav. Chim.*, **76**, 669 (1957). [c] All compounds were analyzed for C, H.

300 ml of H_2O, and 300 ml of Et_2O. The ether layer was separated, dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The residue was triturated with pentane and filtered.

The thioacetonitriles listed in Table II were synthesized by analogous procedures.

Potential Antihypertensive Agents. IV.[1] Unsymmetrically 1,4-Disubstituted Piperazines. II

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In these laboratories, for a number of years, we have been interested in piperazine derivatives as antihypertensive agents. This report presents the syntheses of several 1-alkyl- (or 1-aryl- or 1-aralkyl-) 4-N-substituted carbamoyl- (or thiocarbamoyl-, ureido-, or thioureido-) piperazines and the evaluation of their biological activities.

The compounds prepared and tested in this series are listed in Tables I and II. The N-substituted carbamoyl and thiocarbamoyl derivatives (**1**–**11**, Table I) were obtained by the reaction of the monosubstituted piperazines with the corresponding isocyanates or isothiocyanates in a suitable solvent.

(1) For paper III, see R. N. Prasad, *J. Med. Chem.*, **12**, 290 (1969).

Reaction of 1-methylhomopiperazine with benzyl isothiocyanate, however, gave an oil which could not be induced to crystallize. Treatment of the oil with MeI gave methyl N-benzyl-4-methyl-1-homopiperazinethiocarboximidate (**12**) as a hydriodide salt in 24% over-all yield. Other S-methyl derivatives (**13**, **14**) were prepared from the corresponding thiocarbamoyl derivatives (**7**, **6**) in excellent yields. Reaction of **13** with methanolic NH_3 gave N-cyclohexyl-4-phenyl-1-piperazinecarboxamidine (**15**) in poor yield.

The thioureido and ureido derivatives (**16**–**25**, Table II) were prepared similarly from 1-substituted 4-aminopiperazines. Reaction of some 1-substituted 4-(β-aminoethyl)piperazines with isothiocyanates similarly gave the corresponding thioureas (**26**–**28**, Table II).

Pharmacology.—The piperazines were evaluated for antihypertensive activity by the method reported before.[2] Of these, only **1**, **5**, **6**, and **26** showed a sustained moderate decrease in blood pressure at 5–10 mg/kg. Compounds **4**, **7**, **10**–**12**, **16**, and **20** caused an unsustained fall in blood pressure, whereas **19** produced a transient hypertensive effect. The remaining compounds were inactive.

Experimental Section[3]

Following are representative examples of the preparative methods employed. The solvents used in the preparation and the reaction periods are indicated in Tables I and II.

Method A. 1-(N-Cyclohexylcarbamoyl)-4-phenylpiperazine (1).—A solution of cyclohexyl isocyanate (13.7 g, 0.11 mole) in Et_2O (300 ml) was added dropwise (under anhydrous conditions) to a well-stirred solution of N-phenylpiperazine (16.2 g, 0.1 mole) in C_6H_6 (200 ml) at room temperature. The mixture was refluxed for 0.5 hr and the product was filtered. One recrystallization (C_6H_6) gave the pure product (Table I).

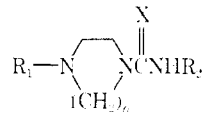
Method B. 1-(N-Benzylthiocarbamoyl)-4-phenylpiperazine (6).—A solution of benzyl isothiocyanate (18.4 g, 0.123 mole) in Et_2O (50 ml) was added to a solution of N-phenylpiperazine (20 g, 0.123 mole) in Et_2O (200 ml) at 10–20°. The mixture was stirred for 0.25 hr, allowed to stand 15 hr at room temperature,

(2) F. Fried, R. N. Prasad, and A. P. Gaunce, *ibid.*, **10**, 279 (1967).

(3) All melting points were determined in open capillary tubes with a Thomas–Hoover capillary melting point apparatus and are corrected. The elemental analyses were performed by Messrs. Orville Kolsto and Victor Rauschel and Staff of Abbott Microanalytical Laboratory, North Chicago, Ill. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

TABLE I

1-SUBSTITUTED 4-N-SUBSTITUTED CARBAMOYL- (OR THIOCARBAMOYL-) PIPERAZINES

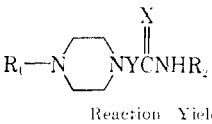


No.	R_1	R_2	n	X	Method[a]	Reaction solvent[b]	Yield, %	Mp, °C	Recrystn solvent[c]	Formula	Analyses
1	C_6H_5	C_6H_{11}	2	O	A (0.5)	E + B	70	137–138.5	B	$C_{17}H_{25}N_3O$	C, H, N
2	C_6H_5	CH_3	2	O	B (1)	E	41	140–143	B	$C_{12}H_{17}N_3O$	C, H, N
3	CH_3	$C_6H_3Cl_2$-3,4	3	O	A (1)	B	78	127–128.5	B	$C_{14}H_{17}Cl_2N_3O$	C, H, Cl, N
4	CH_3	$C_6H_4Cl_2$-3,4	2	O	A (1)	B	77	132.5–133.5	B	$C_{12}H_{13}Cl_2N_3O$	C, H, Cl, N
5	$C_6H_4OCH_3$-o	CH_3	2	O	A (0.5)	E	56	166–167	M + E	$C_{13}H_{19}N_3O_2$	C, H, N, O
6	C_6H_5	$CH_2C_6H_5$	2	S	B (15)	E	32	182–183.5	D + Et	$C_{18}H_{21}N_3S$	C, H, N, S
7	C_6H_5	C_6H_{11}	2	S	B (1)	E	66	188.5–189.5	Et	$C_{17}H_{25}N_3S$	C, H, N, S
8	$C_6H_4OCH_3$-o	C_6H_{11}	2	S	A (1)	E + B	80	170–171	M	$C_{18}H_{27}N_3OS$	C, H, N, S
9	$C_6H_4OCH_3$-o	$CH_2C_6H_5$	2	S	A (1)[d]	B	27	151–152.5	M + D	$C_{19}H_{23}N_3OS$	C, H, N, S
10	CH_3	C_6H_{11}	2	S	A (0.5)	E	78	121.5–123	B	$C_{12}H_{23}N_3S$	C, H, N, S
11	CH_3	$CH_2C_6H_5$	2	S	A (1)	E	81	94–96	B + PE	$C_{13}H_{19}N_3S$	N, S

[a] See Experimental Section for methods. Reaction period (in hours) in parentheses. [b] E = Et_2O, B = C_6H_6. [c] B = C_6H_6, D = DMF, E = Et_2O, Et = EtOH, M = MeOH, PE = petroleum ether (60–80°). [d] The mixture was allowed to stand overnight at room temperature and then the product was filtered.

TABLE II

1-SUBSTITUTED 4-N-SUBSTITUTED UREIDO- (OR THIOUREIDO-) PIPERAZINES



No.	R_1	R_2	Y	X	Method[a]	Reaction solvent[b]	Yield, %	Mp, °C	Recrystn solvent[c]	Formula	Analyses
16	$C_6H_4OCH_3$-o	C_6H_{11}	NH	S	A (2)	E + B	74	184–187	M	$C_{18}H_{28}N_4OS \cdot 0.5H_2O$	C, H, N, S
17	CH_3	C_6H_{11}	NH	S	A (2)[d]	E	62	165–167	B + PE	$C_{12}H_{24}N_3S$	C, H, N, S
18	$C_6H_4OCH_3$-o	$CH_2C_6H_5$	NH	S	A (0.5)	E	71	174–175	M	$C_{19}H_{24}N_4OS$	C, H, N, S
19	CH_3	$CH_2C_6H_5$	NH	S	A (1)	E	60	150–153	B + PE	$C_{13}H_{19}N_3S$	C, H, N, S
20	C_6H_5	$CH_2C_6H_5$	NH	S	C		97	201–202	A + B	$C_{18}H_{22}N_3S$	C, H, N, S
21	CH_3	CH_3	NH	O	B (15)	E	38	143–145	B	$C_7H_{16}N_4O$	C, H, N
22	CH_3	$C_6H_3Cl_2$-3,4	NH	O	A (1)	B	86	189–191	M	$C_{12}H_{16}Cl_2N_4O$	C, H, Cl, N
23	$C_6H_4OCH_3$-o	$C_6H_3Cl_2$-3,4	NH	O	A (0.167)	E	40	211–213	D + W	$C_{18}H_{20}Cl_2N_4O_2$	C, H, Cl, N
24	$C_6H_4OCH_3$-o	CH_3	NH	O	A (0.5)	E	87	135–140	B + E	$C_{13}H_{20}N_4O_2$	C, H, N
25	C_6H_5	CH_3	NH	O	A (4)	E	70	186–187	B	$C_{12}H_{18}N_4O$	C, H, N
26	C_6H_5	$CH_2C_6H_5$	CH_2CH_2NH	S	A (1.5)	B	74	137–138	M	$C_{20}H_{26}N_4S$	C, H, N, S
27	$C_6H_4OCH_3$-o	$CH_2C_6H_5$	CH_2CH_2NH	S	A (1)	B	20	117–119	Et + E	$C_{21}H_{28}N_4OS$	C, H, N, S
28	CH_3	C_6H_{11}	CH_2CH_2NH	S	A (0.5)	E	76	128–130	B + PE	$C_{13}H_{28}N_4S$	C, H, N, S

[a] See Experimental Section for methods. Reaction period (in hours) in parentheses. [b] E = Et_2O, B = C_6H_6. [c] A = Me_2CO, B = C_6H_6, D = DMF, E = Et_2O, Et = EtOH, M = MeOH, PE = petroleum ether (60–80°), W = H_2O. [d] After refluxing for 2 hr the reaction mixture was cooled overnight to isolate the product.

and then filtered. One recrystallization from EtOH and another from alcoholic DMF gave the pure product (Table I).

Methyl N-Benzyl-4-methyl-1-homopiperazinethiocarboximidate Hydriodide (12).—A mixture of benzyl isothiocyanate (6.5 g, 0.0439 mole) and 1-methylhomopiperazine (5.0 g, 0.0439 mole) in Et_2O (100 ml) was refluxed for 2 hr. The clear solution on evaporation gave an oil. The oil was taken up in MeOH (50 ml) and mixed with excess MeI (15 ml), and the mixture was allowed to stand overnight at room temperature. The product (4.4 g, 24% over-all yield from the homopiperazine) was filtered and recrystallized (MeOH), mp 188–190°. *Anal.* ($C_{15}H_{23}N_3S \cdot HI$) C, H, I, N, S.

Methyl N-Cyclohexyl-4-phenyl-1-piperazinethiocarboximidate Hydriodide (13).—A mixture of **7** (3.0 g, 0.01 mole) and MeI (4.26 g, 0.03 mole) in EtOH (50 ml) was refluxed for 2 hr. The clear solution so obtained was evaporated and the residue, on trituration with Et_2O, gave 3.4 g (77%) of the product, mp 166–171°. Recrystallization from MeOH–Et_2O gave the pure product, mp 169–173°. *Anal.* ($C_{18}H_{27}N_3S \cdot HI$) C, H, I, N, S.

Methyl N-benzyl-4-phenyl-1-piperazinethiocarboximidate hydriodide (14) (mp 152–155°, MeOH–Et_2O) was similarly prepared in 70% yield from 1-(N-benzylthiocarbamoyl)-4-phenylpiperazine (**6**) and MeI. *Anal.* ($C_{19}H_{23}N_3S \cdot HI$) C, H, I, N, S.

N-Cyclohexyl-4-phenyl-1-piperazinecarboxamidine Hydrochloride (15).—A solution of **13** (3.0 g, 0.0067 mole) in dry MeOH (15 ml) was mixed with a saturated solution of NH_3 (prepared at 0°) in MeOH (20 ml) and the mixture was allowed to stand at room temperature for 15 hr. The clear solution was then refluxed for 3 hr while NH_3 gas bubbled slowly through the reaction mixture. The reaction mixture was evaporated and the remaining oil was taken up in dry MeOH (70 ml) and passed through a column of Amberlite resin IRA-400 (HCl form). The eluate was evaporated and the residue on trituration with Me_2CO gave the crude product. One recrystallization (MeOH–Et_2O) and another from H_2O gave the pure product in 14% yield, mp 272–273°. *Anal.* ($C_{17}H_{26}N_4 \cdot HCl$) C, H, Cl, N.

Method C. 1-Phenyl-4-(N-benzylthioureido)piperazine (20).—A solution of 1-amino-4-phenylpiperazine (8.85 g, 0.05 mole) in absolute EtOH (190 ml) was heated with a solution of benzyl isothiocyanate (7.45 g, 0.05 mole) in Et_2O (100 ml). When all the Et_2O boiled off, the mixture was refluxed for 3 hr and cooled to room temperature. The product (15.9 g, 97%) was filtered (mp 201–202° dec) and purified by recrystallization from Me_2CO–C_6H_6 (Table II).

Acknowledgment.—The authors wish to express their appreciation to Dr. J. H. Short for many helpful discussions and to Dr. H. Shoepke, Dr. Thomas Darby, Mr. Leo Wiemeler, and Mr. Charles Shannon of the Pharmacology Department of Abbott Laboratories, North Chicago, Illinois, for pharmacological investigations and permission to use their data.