TABLE II

Compd. no.[a]	LD50 mouse, mg./kg. i.p.	Sedative action: Spontaneous motility ED50, mouse, mg./kg. i.p.	Sedative action: Spontaneous motility Rel. activity[b]	Sedative action: Antagonism against DOE ED50 mouse, mg./kg. i.p.	Sedative action: Antagonism against DOE Rel. activity[b]
8	290	100	0.6	60	3.0
9	650	100	0.6	60	3.0
10	700	100	0.6	75	2.4
11	235	80	0.8	200	0.9
12	290	70	0.9	170	1.0
13	255	43	1.5	70	2.5
14	580	77	0.8	200	0.9
15	320	88	0.7	170	1.0
16	400	78	0.8	87	2.0
17	400	35	1.9	55	3.3
Trioxazine	1300	65	1.0	180	1.0

[a] From Table I. [b] Compared with Trioxazine.

Experimental Section

N-[2-(2-Pyridyl)ethyl]-3,4,5-trimethoxybenzamide.—3,4,5-Trimethoxybenzoyl chloride (23.2 g. 0.1 mole) in 250 ml. of benzene was treated with 25 g. of K_2CO_3 and 0.1 mole (12.2 g.) of 2-(β-aminoethyl)pyridine. After being refluxed for 2 hr., the mixture was filtered. From the filtrate, 21 g. (66%) of the base (m.p. 121–122°) was obtained after recrystallization from aqueous ethanol.

Anal. Calcd. for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.23; H, 6.18; N, 8.53.

On acidifying an acetone solution of the base, the **hydrochloride,** m.p. 180–182°, precipitated.

Anal. Calcd. for $C_{17}H_{20}N_2O_4 \cdot HCl$: Cl, 10.05; N, 7.94. Found: Cl, 10.25; N, 7.76.

The **methiodide,** prepared in acetone (24 hr., room temperature), had m.p. 165–167°, yield 86%. Other methiodides were similarly prepared.

Anal. Calcd. for $C_{18}H_{23}IN_2O_4$: I, 27.69; N, 6.11. Found: I, 27.39; N, 5.89.

3-(2-Pyridyl)propyl 3,4,5-Trimethoxybenzoate.—3,4,5-Trimethoxybenzoyl chloride (0.1 mole, 23.1 g.) in 250 ml. of benzene and 0.1 mole (13.7 g.) of 2-(γ-hydroxypropyl)pyridine were left overnight, then refluxed 1 hr. The hydrochloride of the title compound (31 g., 81%) was obtained on filtering the cooled solution; m.p. 158–162° (from ethanol).

Anal. Calcd. for $C_{18}H_{21}NO_5 \cdot HCl$; Cl, 9.64; N, 3.80. Found: Cl, 9.88; N, 4.17.

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Synthesis of 1,4-Disubstituted Piperazines. I[1]

MATTHEW VERDERAME

Chemistry Department, Albany College of Pharmacy, Union University, Albany, New York

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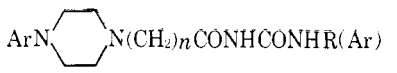
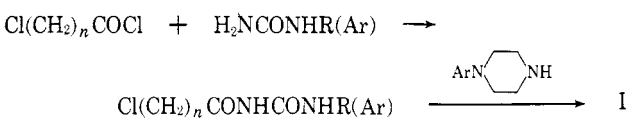
Many new 1,4-disubstituted piperazines of type I have been synthesized as potential pharmacological agents. The acylurea substituent, present in such sedative–hypnotic agents as carbromal, ectylurea, and the barbiturates, attached to the piperazine ring could



I

offer some interesting compounds, since many clinically used piperazines, meclizine, chlorcyclizine, hydroxyzine, and prochlorperazine, function as ataractic, sedative, or antihistaminic agents.

The compounds of structure I, listed in Table II, were synthesized by the reaction sequence indicated below. Data on the chloroacylurea intermediates are presented in Table I.



Biological Data.[2]—The 1,4-disubstituted piperazines were tested for various activities. Compounds **1, 3, 5, 15,** and **16** were inactive in hexobarbital potentiation experiments in mice (loss of righting reflex) at 100 mg./kg. i.p. for 90 sec. However, **2, 4,** and **11** showed minimum activity (40% effective). Among others tested, only **1** gave 40% protection against pentylenetetrazole-induced convulsions at 100 mg./kg. i.p. in mice.

As trichomonacidal agents, **1, 7, 10, 13, 14,** and **16** were ineffective. Compound **2,** however, in a culture tube testing method, arrested the growth of the trichomonads at 1:1000 concentration after incubating for 48 hr. Given *in vivo* against a *T. gallinae* infection in hamsters, **2** enabled 75% of the test animals to clear, as compared with 88% for aminitrazole at 100 mg./kg. *p.o.* Also, against a *T. gallinae* infection in hamsters at 100 mg./kg. *p.o.*, the following compounds gave the following protection: **3,** 25%; **4,** 40%; and, at 200 mg./kg. *p.o.*, **6,** 55%.

Compounds **7, 10, 11, 14,** and **15** were inactive as psychomotor stimulants at 300 mg./kg. *p.o.* in mice. In preventing reserpine ptosis in mice (antidepressant), the minimal significant dose (MSD) for **11** was 50 mg./kg., whereas the MSD for imipramine was 30 mg./kg.

Also, these compounds were tested for various other activities and found to be ineffective. Some of these were anthelmintic, schistosomacidal, antibacterial, antivitamin, antiinflammatory, and antielectroshock.

Experimental Section

The chemicals were purchased from Eastman. All microanalyses were performed at the Sterling-Winthrop Research Institute. 1-Phenylpiperazine[3] and 1-*p*-chlorophenylpiperazine[4] were prepared by a literature method. The chloroacylurea intermediates (Table I) were prepared by combining the N-alkyl- or N-arylureas with the appropriate chloroacyl chloride and warming, if necessary.

1,4-Disubstituted Piperazines (Table II). Procedure A.—The aryl piperazine (2 equiv.) and 1 equiv. of the chloroacylurea were refluxed in alcohol for 0.5–2 hr. The mixture was then

(1) The support of this work by the Sterling-Winthrop Research Institute, Rensselaer, N. Y., is gratefully acknowledged.

(2) The author is indebted to the Biological Division of the Sterling-Winthrop Research Institute for conducting these physiological studies.

(3) C. B. Pollard, *J. Org. Chem.*, **24**, 1175 (1959).

(4) C. B. Pollard and T. H. Wickers, *J. Am. Chem. Soc.*, **76**, 1853 (1954).

TABLE I

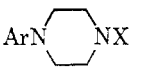
SUBSTITUTED CHLOROACYLUREAS

No.	R	X	Y	Yield, %	M.p., °C. (uncor.)	Recrystn. solvent	Calcd., % Cl	Calcd., % N	Found, % Cl	Found, % N
1a	$ClCH_2$	H	H	47	179–182[a,b]	EtOH–H_2O	...	...	...	...
2a	$ClCH_2$	CH_3	H	52	203–205[c]	EtOH–H_2O	...	...	...	...
3a	$ClCH_2$	C_6H_5	H	50	160–163[d]	EtOH	16.67	13.18	16.99	13.38
4a	$ClCH_2$	C_2H_5	H	48	135–140[e]	EtOH[f]	...	...	...	...
5a	$ClCH_2$	p-$C_2H_5OC_6H_4$	H	76	177–181[g]	AcOH–AcOEt	...	...	...	...
6a	$ClCH_2$	$CH_2CH_2CH_3$	H	51	122–124	CCl_4	19.84	15.68	19.76	15.91
7a	$ClCH_2$	$C(CH_3)_3$	H	40	91–94	EtOH–H_2O	18.41	14.54	18.31	14.31
8a	$ClCH_2$	C_6H_5	C_6H_5	53	146–150	AcOEt	[h]			
9a	$ClCH_2$	m-$CH_3C_6H_4$	H	79	122–124	CCl_4	15.65	12.37	15.83	12.46
10a	$ClCH_2$	$CH_2CH{=}CH_2$	H	54	113–116	Acetone[i]	20.08	15.86	19.84	15.57
11a	$ClCH_2CH_2$	H	H	46	180–181	EtOH	23.55	18.61	23.75	18.68

[a] D. Tommasi [*Bull. soc. chim. France*, [2] **19**, 243 (1873)] reports m.p. 160° dec. [b] E. I. Hoegberg [*Chem. Abstr.*, **46**, 1585 (1952)] reports m.p. 182–185°. [c] H. Aspelund [*Finska Kemistsamfundets Medd.*, **49**, 49 (1940); *Chem. Abstr.*, **35**, 2144 (1941)] reports m.p. 201–202°. [d] E. I. Hoegberg [U. S. Patent 2,562,863 (1951); *Chem. Abstr.*, **46**, 1585 (1952)] reports m.p. 149–153°. [e] R. Andreasch [*Monatsh.*, **43**, 485 (1923); *Chem. Abstr.*, **17**, 1429 (1923)] reports m.p. 138°. [f] CCl_4 may also be used. [g] C. Alberti [*Gazz. chim. ital.*, **69**, 150 (1939); *Chem. Abstr.*, **33**, 7283 (1939)] reports m.p. 181–182°. [h] This compound did not show a correct analysis but was successfully used in a subsequent reaction. [i] Ethyl acetate plus $CHCl_3$ may also be used.

TABLE II

1,4-DISUBSTITUTED PIPERAZINES



No.	Ar	X	Yield, %	M.p., °C.[a]	Procedure[b]	Reaction time, hr.	Recrystn. solvent[c]	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
1	C_6H_5	$CH_2CONHCONH_2$	92	198.2–199.4	A	2	A + B	$C_{13}H_{13}N_4O_2$	59.52	6.92	21.36	59.83	6.77	21.06
2	C_6H_5	$CH_2CONHCONHCH_3$	66	164.2–166.2	A	0.5	A	$C_{14}H_{16}N_4O_2$	60.85	7.29	20.08	61.13	7.13	20.22
3	C_6H_5	$CH_2CONHCONHC_6H_5$	74	135.2–136.8	A	2	A	$C_{19}H_{20}N_4O_2$	67.43	6.55	16.56	67.70	6.59	16.22
4	C_6H_5	$CH_2CONHCONHC_2H_5$	60	118.2–119.8	A	1	A + B	$C_{15}H_{22}N_4O_2$	62.04	7.64	19.30	62.01	7.55	19.07
5	C_6H_5	$CH_2CONHCONHC_6H_4OC_2H_5$-$p$	30	171.4–172.8	A	0.5	C	$C_{21}H_{26}N_4O_3$	65.95	6.85	14.65	66.09	6.71	14.64
6	C_6H_5	$CH_2CONHCONHCH_2CH_2CH_3$	75	97.2–99.0	B	1	A + B	$C_{16}H_{24}N_4O_2$	63.13	7.95	18.41	63.05	8.26	18.54
7	C_6H_5	$CH_2CONHCONHC(CH_3)_3$	38	121.2–122.0	A	1	F + G	$C_{17}H_{26}N_4O_2$	64.12	8.23	17.60	64.54	7.92	17.77
8	C_6H_5	$CH_2CONHCON(C_6H_5)_2$	29	180.0–182.4	A	1.5	C	$C_{25}H_{26}N_4O_2$	72.44	6.32	13.52	72.28	6.30	13.63
9	C_6H_5	$CH_2CONHCONHC_6H_4CH_3$-m	39	126.2–132.2	A	0.8	A	$C_{20}H_{24}N_4O_2$	68.16	6.86	15.90	68.13	6.61	15.81
10	C_6H_4Cl	$CH_2CONHCONHCH_2CH{=}CH_2$	62	147.2–150.2	B	1.8	C	$C_{16}H_{21}ClN_4O_2$[d]	...	...	16.64	...	...	16.65
11	C_6H_4Cl	$CH_2C(Br){=}CH_2$[e]	22	84.2–85.8	B	1	A (1st) H (2nd)	$C_{13}H_{16}BrClN_2$[f]	...	...	8.88	...	...	8.58
12	C_6H_4Cl	$CH_2CH_2CONHCONH_2 \cdot HCl$	54	220–222	B	1	B + E	$C_{14}H_{20}Cl_2N_4O_2$[g]	48.41	5.84	...	48.16	5.93	...
13	C_6H_4Cl	$CH_2CONHCONHC_6H_5$	50	191.4–193.8	B	1.5	C + D	$C_{19}H_{21}ClN_4O_2$[h]	...	...	15.03	...	...	15.33
14	C_6H_4Cl	$CH_2CONHCONHCH_3$	65	206.0–208.0	B	1	D + A	$C_{14}H_{19}ClN_4O_2$[i]	...	...	18.03	...	...	18.33
15	C_6H_5		55	202.2–203.2	A	0.5	D + E	$C_{24}H_{28}N_8OS$[j]	71.79	5.77	10.47	72.47	5.80	10.18
16	C_6H_5	$CONHC_6H_5$	52	188.2–191.2[k]		0.5	A	$C_{17}H_{19}N_3O$	72.57	6.81	14.94	72.81	6.57	14.60

[a] Melting points (corrected) were taken on a Hershberg apparatus. [b] These procedures are described in the Experimental Section. [c] A, alcohol; B, water; C, ethyl acetate; D, acetic acid; E, acetone; F, carbon tetrachloride; G, petroleum ether (b.p. 30–80°); H, methanol. [d] *Anal.* Calcd.: Cl, 10.53. Found. Cl, 10.70. [e] Derived from 2,3-dibromopropene. [f] *Anal.* Calcd.: Br, 25.32. Found: Br, 25.42. [g] *Anal.* Calcd.: Cl, 20.42. Found: Cl, 20.32. [h] *Anal.* Calcd.: Cl, 9.51. Found: Cl, 9.82. [i] *Anal.* Calcd.: Cl, 11.41. Found: Cl, 11.52. [j] *Anal.* Calcd.: S, 7.99. Found: S, 7.68. [k] This compound was prepared by combining 1 equiv. each of phenyl isocyanate and 1-phenylpiperazine in absolute ether.

chilled, and the amine hydrochloride was separated. Evaporation of the alcohol under reduced pressure usually left an oil which was dissolved in dilute HCl. The solution was filtered to remove insoluble impurities, chilled, and made alkaline with dilute NaOH. Final purification was effected by the use of the appropriate solvent listed in Table II.

Procedure B.—The aryl piperazine and the alkylating agent (1 equiv. each) were combined and warmed in aqueous alcohol which contained $NaHCO_3$ as the HCl acceptor. The reaction time varied from 1–1.5 hr. The product resulting after evaporation of the alcohol under diminished pressure was dissolved in dilute HCl. The solution was filtered and made alkaline with aqueous NaOH. The recrystallization solvents are listed in Table II.

Compound **13** precipitated as a hydrochloride salt. The average yields of the two methods were comparable.