5-halomethylpyrimidine, 0.0070 mole of 5-(2-hydroxyethyl)-4-methylthiazole,[14] and 5 ml. of light paraffin oil was used. The reaction products were isolated essentially by the method reported earlier for XII.[3] The products from the 5-bromomethylpyrimidines gave negative bromide tests and were used for the analytical samples after purification by dissolving in ethanol and adding ethanol-hydrogen chloride. These samples had the same melting points as those obtained from the respective 5-chloromethylpyrimidines and the mixed melting points showed no depression.

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DEPARTMENT OF CHEMISTRY
FAIRFIELD UNIVERSITY
FAIRFIELD, CONN.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF BUFFALO
BUFFALO 14, N. Y.

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(13) G. A. Stein, *et al.*, *J. Am. Chem. Soc.*, **63**, 2059 (1941).

(14) The authors are grateful to Dr. Max Tishler and Dr. Anthony H. Land, Merck Sharp and Dohme Research Laboratories, for a sample of this compound.

Alkyl- and Arylthiomethylpiperazines

C. B. POLLARD[1] AND D. E. BUTLER[2]

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In continuation of our research in the field of piperazine chemistry, we have prepared a series of alkyl- and arylthiomethylpiperazines. Analogous compounds have been prepared by others[3-5] by condensing secondary amines with formaldehyde and a thiol using anhydrous potassium carbonate to absorb the water formed. In preparing this series, we have used minor modifications of the methods used by these investigators.

$$R_2NH + HCHO + R'SH \longrightarrow R_2CH_2SR' + H_2O$$

Utilization of an arenethiol in this reaction could theoretically lead to compounds of this same chemical class or to Mannich bases of the type produced with phenols, but Grillot and coworkers[5] have shown that aryldialkylaminomethyl sulfides are ordinarily formed. Our findings have confirmed their results.

A total of forty-eight compounds were prepared, using ethane-, butane-, benzene-, and *p*-toluenethiols and a series of twelve piperazines. Physical data on these compounds are compiled in Tables I and II. The compounds have been submitted to Parke, Davis and Co. for pharmacological screening.

EXPERIMENTAL

Preparation of alkyl- and arylthiomethylpiperazines. The thiol was added dropwise with stirring to an equivalent

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(1) Deceased.

(2) Present address: Parke, Davis and Co. Research Laboratories, Ann Arbor, Mich.

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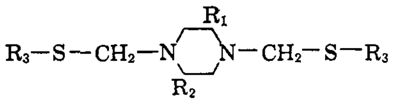
TABLE I

ALKYLTHIOMETHYLPIPERAZINES



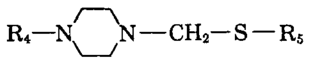
						Analyses[b]			
						Carbon, %		Hydrogen, %	
R_1	R_2	R_3	B.P. or M.P.[a]	Yield, %	n_D^{25}	Calcd.	Found	Calcd.	Found
H—	H—	C_2H_5—	140–141(0.30)	40	1.5314	51.24	51.60	9.46	9.28
H—	CH_3—	C_2H_5—	126–126.5 (0.40)	32	1.5283	53.18	53.42	9.74	9.61
CH_3—	CH_3—	C_2H_5—	57.1–58.8	49		54.91	54.72	9.99	9.98
H—	H—	*n*-C_4H_9—	43.5–46.6	52		57.89	57.90	10.41	10.05
H—	CH_3—	*n*-C_4H_9—	157–158 (0.075)	54	1.5157	59.14	59.11	10.59	10.34
CH_3—	CH_3—	*n*-C_4H_9—	32.4–34.5	48		60.33	60.42	10.76	10.62
H—	H—	C_6H_5—	100–102.9	55		65.42	65.70	6.71	7.01
H—	CH_3—	C_6H_5—	43.5–46.6	52		66.23	66.18	7.02	7.12
CH_3—	CH_3—	C_6H_5—	97.0–98.0	48		67.00	67.10	7.31	7.21
H—	H—	*p*-CH_3—C_6H_4—	127.3–130.4	84		67.00	67.30	7.31	7.68
H—	CH_3—	*p*-CH_3—C_6H_4—	68.7–70.8	69		67.72	67.45	7.58	7.55
CH_3—	CH_3—	*p*-CH_3—C_6H_4—	135.3–137.4	62		68.35	68.36	7.82	7.78

[a] Figure in parentheses represents pressure (mm.) at which distillation was carried out and all melting points are corrected.

[b] Analyses for N% and S% also checked.

TABLE II

ARYLTHIOMETHYLPIPERAZINES



					Analyses[b]			
					Carbon, %		Hydrogen, %	
R_4	R_5	B.P. or M.P.[a]	Yield, %	n_D^{25}	Calcd.	Found	Calcd.	Found
C_6H_5—	C_2H_5—	79.8–81.9	64		66.06	65.95	8.53	8.42
o-CH_3—C_6H_4—	C_2H_5—	158–158.5(0.40)	52	1.5617	67.16	67.40	8.86	9.29
m-CH_3—C_6H_4—	C_2H_5—	172–174(0.30)	41	1.5723	67.16	67.50	8.86	8.85
p-CH_3—C_6H_4—	C_2H_5—	29.0–30.5	52		67.16	67.39	8.86	8.74
o-Cl—C_6H_4—	C_2H_5—	158–158.5(0.30)	57		57.65	57.70	7.07	6.65
m-Cl—C_6H_4—	C_2H_5—	185.5–186(0.50)	45	1.5879	57.65	57.80	7.04	6.65
p-Cl—C_6H_4—	C_2H_5—	68.7–71.8	42		57.65	57.65	7.04	7.14
o-CH_3O—C_6H_4—	C_2H_5—	180–180.5(1.30)	62	1.5704	63.12	63.30	8.32	8.17
CH_3—	C_2H_5=	76.0–78(0.70)	64	1.5008	55.12	55.01	10.41	10.39
C_6H_5—	*n*-C_4H_9—	179–180(0.70)	58	1.5637	68.13	68.19	9.15	9.11
o-CH_3—C_6H_4—	*n*-C_4H_9—	160–160.5(0.17)	64	1.5501	69.53	69.31	8.75	9.18
m-CH_3—C_6H_4—	*n*-C_4H_9—	167.5–168(0.20)	46	1.5590	69.53	69.21	8.75	9.01
p-CH_3—C_6H_4—	*n*-C_4H_9—	28.3–30.6	54		69.53	69.31	8.75	9.04
o-Cl—C_6H_4—	*n*-C_4H_9—	178–178.5(0.15)	48	1.5634	60.27	60.44	7.75	7.68
m-Cl—C_6H_4—	*n*-C_4H_9—	179.5–180(0.15)	72	1.5721	60.27	60.11	7.75	7.79
p-Cl-C_6H_4—	*n*-C_4H_9—	47.2–51.1	47		60.27	60.09	7.75	7.76
o-CH_3O—C_6H_4—	*n*-C_4H_9—	180–180.5(0.20)	57	1.5583	65.28	65.21	8.90	8.65
CH_3—	*n*-C_4H_9—	89–90(0.18)	62	1.4933	59.34	59.30	10.96	10.79
C_6H_5—	C_6H_5—	75.8–78.3	76		71.80	71.51	7.09	6.94
o-CH_3—C_6H_4—	C_6H_5—	55.6–57.7	49		72.45	72.40	7.43	7.14
m-CH_3—C_6H_4—	C_6H_5—	84.9–87.1	82		72.45	72.20	7.43	7.17
p-CH_3—C_6H_4—	C_6H_5—	138.9–141.4	81		72.45	72.25	7.43	7.49
o-Cl-C_6H_4—	C_6H_5—	52.6–56.5	63		64.03	64.21	6.01	6.06
m-Cl-C_6H_4—	C_6H_5—	101–103.1	79		64.03	64.10	6.01	5.65
p-Cl-C_6H_4—	C_6H_5—	83.9–85.0	75		64.03	64.00	6.01	6.26.
o-CH_3O—C_6H_4—	C_6H_5—	67.2–71.1	50		68.75	68.70	7.06	7.13
CH_3—	C_6H_5—	112–113(0.15)	48	1.5734	64.80	64.91	8.16	8.02
C_6H_5—	*p*-CH_3—C_6H_4—	100–101.1	85		72.45	72.45	7.43	7.46
o-CH_3—C_6H_4—	*p*-CH_3—C_6H_4—	56.6–58.7	73		73.02	73.00	7.74	7.54
m-CH_3—C_6H_4—	*p*-CH_3—C_6H_4—	63–64.5	72		73.02	73.11	7.74	7.89
p-CH_3—C_6H_4—	*p*-CH_3—C_6H_4—	138.4–139.9	68		73.02	72.65	7.74	7.54
o-Cl—C_6H_4—	*p*-CH_3—C_6H_4—	66.0–68.0	78		64.95	64.96	6.36	6.36
m-Cl—C_6H_4—	*p*-CH_3—C_6H_4—	67.7–69.8	81		64.95	64.98	6.36	6.53
p-Cl—C_6H_4—	*p*-CH_3—C_6H_4—	103.1–105.2	81		64.95	65.39	6.36	6.25
o-CH_3O—C_6H_4—	*p*-CH_3—C_6H_4—	48.5–51.6	69		69.45	69.30	7.36	7.42
CH_3—	*p*-CH_3—C_6H_4—	33.4–36.5	36		66.06	66.15	8.53	8.52

[a, b] The same as in Table I.

amount of the piperazine (previously melted if necessary), causing in some cases a precipitation of an addition product. To this mixture was added an equivalent amount of 37% formaldehyde, and the mixture was refluxed with stirring for 3 hr. After cooling to room temperature, the product was extracted with ether. The ether extracts were combined and dried over anhydrous potassium carbonate. The ethereal solution was filtered and then passed over a column of aluminum oxide (Woelm, neutral, activity grade 1 for chromatography). The ether was removed at reduced pressure. If the residue crystallized, it was further purified by recrystallization from anhydrous ether, methanol, or ethanol. The oils were distilled at reduced pressures.

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DEPARTMENT OF CHEMISTRY
UNIVERSITY OF FLORIDA
GAINESVILLE, FLA.

Some Glycosyl Derivatives of Piperazine

C. G. C. CATESBY[1] AND A. M. STEPHEN[2]

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Piperazine derivatives are of current interest because they display a diversity of pharmacological properties,[3] and the biological importance of such glycosylamines as the nucleosides has long been

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[1] Present address: African Explosives Research Department, Northrand, Transvaal, South Africa.

[2] On leave at the Department of Agricultural Biochemistry, University of Minnesota, St. Paul, Minn.

[3] *The Dispensatory of the United States of America*, A. Osol and G. E. Farrar, Jr., ed., Lippincott Co., Philadelphia, 1955, p. 1807; M. Harfenist and E. Magnien, *J. Am. Chem. Soc.*, 80, 6257 (1958) and earlier papers.