

TABLE I
1-BROMO-4-DIALKYLAMINOBUTAN-2-ONE HYDROBROMIDES $RCH_2CH_2COCH_2Br \cdot HBr$

R	M.P., C°	YIELD, %	FORMULA	ANALYSIS									
				Calc'd				Found					
				C	H	Br	C	H	Br	C	H	Br	
$(CH_3)_2N^a$	84-85	16	$C_8H_{13}Br_2NO \cdot H_2O$	4.80 (N)	4.80 (N)	27.37 ^b	4.78 (N)	4.78 (N)	27.25	4.78 (N)	27.25	4.78 (N)	27.25
$(C_2H_5)_2N$	82-83	36	$C_8H_{17}Br_2NO$	4.62 (N)	4.62 (N)	52.74	4.79 (N)	4.79 (N)	52.40	4.79 (N)	52.40	4.79 (N)	52.40
$(n-C_4H_9)_2N$	114.5-115.5	38	$C_{10}H_{21}Br_2NO$	6.39	6.39	48.27	6.39	6.39	47.96	6.39	47.96	6.39	47.96
$(iso-C_4H_9)_2N$	143-143.5	42	$C_{10}H_{21}Br_2NO$	36.27	36.27	36.10	36.10	36.10	36.10	36.10	36.10	36.10	36.10
$(n-C_4H_9)_2N$	126.5-127.5	61	$C_{12}H_{25}Br_2NO$	40.13	40.13	3.90 (N)	40.02	40.02	3.78 (N)	40.02	3.78 (N)	40.02	3.78 (N)
$C_2H_5N^c$	157-158	55	$C_8H_{13}Br_2NO_2$	4.42 (N)	4.42 (N)	25.18 ^b	4.68 (N)	4.68 (N)	25.44	4.68 (N)	25.44	4.68 (N)	25.44
C_4H_9NO	164-165	68	$C_8H_{13}Br_2NO_2$	4.42 (N)	4.42 (N)	25.18 ^b	4.68 (N)	4.68 (N)	25.44	4.68 (N)	25.44	4.68 (N)	25.44

^a Mannich (5) reported m.p. 103° for the anhydrous material. ^b Ionic halogen. ^c See ref. (2) and (4).

TABLE II

2-ARYLOXYMETHYL-4-(2-DIALKYLAMINOETHYL)THIAZOLE DIHYDROBROMIDES $\text{AROCH}_2\text{C} \begin{array}{l} \diagup \text{S-CH} \\ \diagdown \text{N-CCH}_2\text{CH}_2\text{R} \end{array} \cdot 2\text{HBr}$

ArO	R	M.P., C. ^a	YIELD, %	FORMULA	ANALYSES					
					Calc'd			Found		
					C	H	Br	C	H	Br
Phenoxy	Morpholino	205-207	60	$\text{C}_{16}\text{H}_{22}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	41.21	4.76	34.28	41.52	5.08	33.77
<i>p</i> -Toloxy	"	193-195	71	$\text{C}_{17}\text{H}_{24}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	42.51	5.04	33.28	41.99	5.45	33.26
2,5-Dimethylphenoxy	"	208-210	38	$\text{C}_{18}\text{H}_{26}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	43.73	5.30	32.34	43.96	5.71	32.44
<i>o</i> -Isopropylphenoxy	"	207-209	38	$\text{C}_{19}\text{H}_{28}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	44.89	5.55	31.44	44.80	5.75	31.66
Thymoxy	"	199-200	47	$\text{C}_{20}\text{H}_{30}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	45.98	5.79	30.60	45.55	5.74	30.01
<i>p</i> -Diphenyloxy ^a	"	193-194	57	$\text{C}_{22}\text{H}_{26}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	57.26	5.46	17.32	57.44	5.16	16.80
<i>m</i> -Chlorophenoxy	"	193-195	57	$\text{C}_{16}\text{H}_{21}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	38.38	4.23	31.92	37.95	4.44	31.90
<i>p</i> -Chlorophenoxy	"	222-224	68	$\text{C}_{16}\text{H}_{21}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	38.38	4.23	31.92	38.72	4.47	32.03
Phenoxy	Piperidino	232-234	67	$\text{C}_{17}\text{H}_{23}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	40.94	4.65	32.05	41.36	4.82	31.68
<i>p</i> -Toloxy	Diethylamino	173-174	73	$\text{C}_{16}\text{H}_{24}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	42.48	5.35	35.34	42.59	5.42	34.89
2,5-Dimethylphenoxy	"	182-184	69	$\text{C}_{17}\text{H}_{26}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	43.78	5.62	34.28	44.07	5.60	33.84
<i>o</i> -Isopropylphenoxy	"	172-174	73	$\text{C}_{18}\text{H}_{28}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	45.01	5.88	33.28	44.67	6.14	33.63
Thymoxy	"	184-186	36	$\text{C}_{19}\text{H}_{30}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	46.16	6.12	32.33	46.01	5.78	31.83
<i>m</i> -Chlorophenoxy	"	202-204	76	$\text{C}_{20}\text{H}_{32}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	47.25	6.35	31.44	47.66	6.04	31.71
<i>p</i> -Chlorophenoxy	"	188-190	73	$\text{C}_{16}\text{H}_{23}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	39.48	4.76	32.84	39.47	4.59	32.42
Phenoxy	Diethylamino	196-197	73	$\text{C}_{16}\text{H}_{23}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	39.48	4.76	32.84	39.73	4.63	32.36
<i>p</i> -Toloxy	"	183-185	43	$\text{C}_{17}\text{H}_{25}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	50.00	5.34	30.26	49.93	5.04	29.86
2,5-Dimethylphenoxy	"	172-173	69	$\text{C}_{18}\text{H}_{27}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	45.00	5.88	33.27	45.32	6.09	33.38
<i>o</i> -Isopropylphenoxy	"	166-168	66	$\text{C}_{19}\text{H}_{29}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	46.15	6.12	32.33	45.73	6.08	32.09
Thymoxy	"	152-154	68	$\text{C}_{20}\text{H}_{31}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	47.24	6.35	31.44	47.03	6.61	31.70
<i>p</i> -Diphenyloxy ^a	"	164-166	62	$\text{C}_{21}\text{H}_{33}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	48.28	6.56	30.60	48.58	6.41	30.96
<i>m</i> -Chlorophenoxy	"	159-161	51	$\text{C}_{22}\text{H}_{35}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	49.26	6.77	29.84	49.62	6.76	29.65
<i>p</i> -Chlorophenoxy	"	125-127	62	$\text{C}_{18}\text{H}_{27}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	60.62	6.57	16.81	60.67	6.73	16.31
<i>p</i> -Chlorophenoxy	"	137-138	91	$\text{C}_{18}\text{H}_{27}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	42.00	5.29	31.05	41.95	5.56	30.77
Phenoxy	Di- <i>n</i> -butylamino	182-184	48	$\text{C}_{20}\text{H}_{32}\text{Br}_2\text{N}_2\text{O}_2\text{S}$	47.25	6.35	31.44	46.83	6.58	31.86
<i>p</i> -Chlorophenoxy	Di- <i>n</i> -butylamino	173-175	74	$\text{C}_{20}\text{H}_{31}\text{Br}_2\text{ClN}_2\text{O}_2\text{S}$	44.25	5.76	29.45	43.71	5.91	29.28

^a Monohydrobromide.

TABLE III



R	M.P., C°	YIELD, %	FORMULA	ANALYSIS					
				Calc'd			Found		
				C	H	Br	C	H	Br
Morpholino	252-254	32	C ₉ H ₁₆ Br ₂ N ₂ OS	30.01	4.48	7.78 (N)	30.29	5.13	7.54 (N)
Piperidino	271-272	38	C ₁₀ H ₁₈ Br ₂ N ₂ S	26.43	7.82 (N)	44.63	26.56	7.97 (N)	45.18
Dimethylamino	235-237	37	C ₇ H ₁₄ Br ₂ N ₂ S	31.23	4.43	8.81 (N)	31.14	4.47	8.45 (N)
Diethylamino	253-254	29	C ₉ H ₁₈ Br ₂ N ₂ S		5.24	46.18		5.26	46.20
Di- <i>n</i> -propylamino	196.5-197	47	C ₁₁ H ₂₂ Br ₂ N ₂ S		7.49 (N)	42.71		7.81 (N)	42.50
Di-isopropylamino	238-239	69	C ₁₁ H ₂₂ Br ₂ N ₂ S		7.49 (N)	42.71		7.67 (N)	42.34

TABLE IV

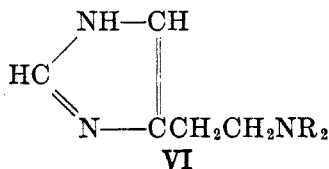
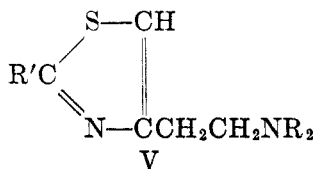
$$\begin{array}{c}
 \text{S-CH} \\
 \parallel \\
 \text{R'NHC} \\
 \parallel \\
 \text{N-CCH}_2\text{CH}_2\text{R}
 \end{array}
 \cdot 2\text{HBr}$$

2-(N-ALKYLAMINO)-4-(2-DIALKYLAMINOETHYL)THIAZOLE DIHYDROBROMIDES

R'	R	M.P., C°	YIELD, %	FORMULA	ANALYSIS					
					Calc'd			Found		
					C	H	N	C	H	N
Allyl.....	Morpholino	185.5-186.5	75	C ₁₂ H ₂₁ Br ₂ N ₃ OS	34.71	5.10	10.12	34.66	4.73	9.82
Anilino.....	"	204-205	70	C ₁₈ H ₂₁ Br ₂ N ₃ OS	39.93	4.69	9.03	39.38	4.72	8.88
Benzyl.....	"	193.5-195.5	91	C ₁₆ H ₂₃ Br ₂ N ₃ OS	41.30	4.98	9.35	41.08	5.49	9.44
Anilino.....	Piperidino	208-210	78	C ₁₄ H ₂₃ Br ₂ N ₃ S	42.77	5.16	9.35	42.71	5.07	9.44
Benzyl.....	"	206.5-208	67	C ₁₇ H ₂₃ Br ₂ N ₃ S	44.07	5.44	9.35	44.11	5.60	9.44
Allyl.....	Diethylamino	190-191	61	C ₁₂ H ₂₃ Cl ₂ N ₃ S ^a	46.15	7.42	13.45	46.56	7.22	12.95
Anilino.....	"	176.5-177	75	C ₁₆ H ₂₃ Br ₂ N ₃ S	41.20	5.30	9.61	41.22	5.38	9.72
Allyl.....	Di-n-propylamino	192.5-193	55	C ₁₄ H ₂₇ Br ₂ N ₃ S	39.17	6.34	9.81	39.37	6.16	9.52
Anilino.....	"	136-138	70	C ₁₇ H ₂₇ Br ₂ N ₃ S	43.88	5.85	9.03	44.83	6.04	9.00
Benzyl.....	"	185-187	45	C ₁₈ H ₂₉ Br ₂ N ₃ S	45.10	6.10	8.77	45.06	6.20	8.73
Allyl.....	Di-isopropylamino	177-178	87	C ₁₄ H ₂₇ Br ₂ N ₃ S		7.47 (S)	9.79		7.45 (S)	9.63
Anilino.....	"	159-160	60	C ₁₇ H ₂₇ Br ₂ N ₃ S		34.35 (Br)	9.03		34.16 (Br)	9.17
Allyl.....	Di-n-butylamino	175.5-177	46	C ₁₆ H ₃₁ Br ₂ N ₃ S	42.02	6.83	9.19	42.61	6.32	9.29

^a Dihydrochloride.

thioformamide and III, in order to be compared with the corresponding imidazoles (VI), which have recently been prepared in this laboratory (6). Finally, several N-substituted thioureas (allyl, phenyl, benzyl) were condensed with the brominated "Mannich bases" (III) thus affording a series of N-substituted 2-amino-4-(2-dialkylaminoethyl)thiazoles (V, R' = NHR') (Table IV).



EXPERIMENTAL²

4-Dialkylaminobutan-2-ones ("Mannich Bases") $R_2NCH_2CH_2COCH_3$, R = CH₃ (7), C₂H₅ (7, 8), n-C₃H₇ (7), n-C₄H₉ (7), piperidine (R₂N) (9), and morpholine (R₂N) (10), were prepared by the Mannich reaction (3) from the amine hydrochloride, formalin solution, and acetone. The use of methyl vinyl ketone is illustrated with diisopropylamine:

A mixture of 38 g. of methyl vinyl ketone (85% azeotrope) and 50.5 g. of diisopropylamine was heated for six hours on the steam-bath and the upper layer was separated and distilled; 39.6 g. (46%) of 4-diisopropylaminobutan-2-one, b.p. 95-99° at 12 mm. was obtained.

Anal. Calc'd for C₁₀H₂₁NO: Neut. equiv., 171.3. Found: Neut. equiv., 175.2.

1-Bromo-4-dialkylaminobutan-2-one hydrobromides (III). The bromination of the "Mannich bases" was conducted in 35-40% hydrogen bromide-acetic acid solution (2, 5) except that the reaction mixture was cooled rather than warmed (2). Such a procedure or the use of pyridine hydrobromide perbromide (4) invariably led to colorless material. The pertinent information is summarized in Table I.

Preparation of thiazoles. The following procedure is typical: To a hot solution of 20.2 g. of phenoxyacetothioamide (1) in ethanol was added in one portion 40 g. of 1-bromo-4-di-n-propylaminobutan-2-one hydrobromide and the mixture was shaken while warm until all the hydrobromide was dissolved. After gradual cooling to room temperature, the product was partially precipitated by the addition of ca. one-fifth the volume of anhydrous ether. The crude material (42.1 g., m.p. 170-173° with previous sintering) was recrystallized from ethanol-ether and afforded 40 g. (69%) of colorless crystals of 2-phenoxyethyl-4-(2-di-n-propylaminoethyl)thiazole dihydrobromide (Table II) melting at 172-173°. In a few instances (Table IV), the dihydrobromide was oily, whereupon it was converted to the free base and thence the hydrochloride. In the preparation of 2-unsubstituted thiazoles (Table III), the thioformamide represented a 1:1 mixture of formamide and thioformamide (11) and hence a proportionately larger amount had to be used. The formamide presented no complication in the isolation procedure since it remained in solution.

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SUMMARY

1-Bromo-4-dialkylaminobutan-2-one hydrobromides, obtainable from the corresponding "Mannich bases", were condensed with (a) aryloxyacetothioamides to yield a series of 2-(aryloxyethyl)-4-(2-dialkylaminoethyl)thiazole dihydro-

² The microanalyses were performed by G. L. Stragand, Microchemical Laboratory, University of Pittsburgh.

bromides; (b) thioformamide, to give the corresponding 2-unsubstituted thiazole derivatives; and (c) N-alkylated thioureas, to provide the N-monosubstituted 2-amino-4-(2-dialkylaminoethyl)thiazole dihydrobromides.

SUMMIT, N. J.

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