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2-(ARYLOXYMETHYL)THIAZOLINES AND PENTHIAZOLINES

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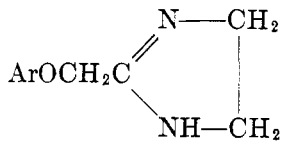
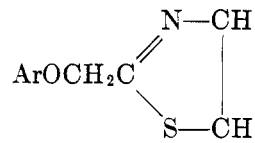
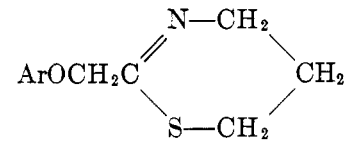
In continuation of earlier work (1, 2) on 2-(aryloxymethyl)imidazoline derivatives (I), we investigated the effect on pharmacological activity of replacing one of the nitrogen atoms by sulfur. The present report deals with the synthesis of such 2-(aryloxymethyl)thiazolines (II) and their six-membered homologs, the penthiazolines (dihydrothiazines) (III); the pharmacological evaluation of these compounds will be reported elsewhere by Dr. B. N. Craver and colleagues from our Division of Macrobiology.



I



II



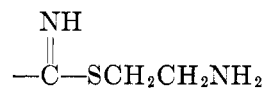
III

METHOD A

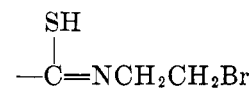
The aryloxyacetonitriles (IV) described previously (1) were converted in high yield to the corresponding acetothioamides (V) (Table I) in the usual manner (3) with ammonia and hydrogen sulfide in alcohol solution. Fusion of the thioamides with 2-bromoethyl- or 3-bromopropyl-amine hydrobromide according to the procedure of Gabriel and Hirsch (4) led to the respective thiazoline (II) (Table IV) and penthiazoline derivatives (III) (Table V). In most instances, higher yields were obtained in the penthiazoline series. All compounds were isolated and characterized as their picrates. For biological testing, the picrates were converted to the free bases and thence to the water-soluble hydrochlorides.

$$\underset{\text{IV}}{ArOCH_2CN} \rightarrow \underset{\text{V}}{ArOCH_2CSNH_2} \xrightarrow[n = 2 \text{ or } 3]{Br(CH_2)_nNH_2 \cdot HBr} \text{II or III}$$

The reaction presumably involves as an intermediate (A) or (B) (5) rather than (C), since the latter would give rise to the imidazoline (I) by the Forssel reaction (6).



(A)



(B)

(C)

METHOD B

As an alternate route to the desired heterocyclics, 2-bromoethyl- (VII) (Table II) or 3-bromopropyl-aryloxyacetamides (VIII) (Table III) were refluxed in

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TABLE I

ARYLOXYACETOTHIOAMIDES $ArOCH_2CSNH_2$

ArO	M.P., °C.	YIELD, %	FORMULA	ANALYSIS			
				N		S	
				Calc'd	Found	Calc'd	Found
Phenoxy[a]	112–113	96	C_8H_9NOS	8.38	8.44	19.17	19.16
o-Toloxy	131–132	91	$C_9H_{11}NOS$	7.73	7.84	17.69	18.26
p-Toloxy	118–120	93	$C_9H_{11}NOS$	7.73	7.73	17.69	17.22
2,5-Dimethylphenoxy	148–150	86	$C_{10}H_{13}NOS$	7.17	6.97	16.42	16.45
o-Isopropylphenoxy	120–121	82	$C_{11}H_{15}NOS$	6.69	7.09	15.32	15.20
Thymoxy	134–135	74	$C_{12}H_{17}NOS$	6.27	6.63	14.36	14.37
Carvacryloxy	82–84	79	$C_{12}H_{17}NOS$	6.27	6.80	14.36	14.58
p-Chlorophenoxy	105–107	93	C_8H_8ClNOS	6.96	6.88	15.90	15.55
m-Chlorophenoxy	124–125	93	C_8H_8ClNOS	6.96	6.84	15.90	16.24
p-Diphenyloxy	186–188	95	$C_{14}H_{13}NOS$	5.76	5.73	13.18	12.93

[a] Fritzsche, *J. prakt. Chem.* [N.F.] **20**, 267 (1879), reported m.p. 111°.

TABLE II

2-BROMOETHYLARYLOXYACETAMIDES $ArOCH_2CONHCH_2CH_2Br$

ArO	M.P., °C.	YIELD, %	FORMULA	ANALYSIS			
				N		Br	
				Calc'd	Found	Calc'd	Found
Phenoxy	75–77	52	$C_{10}H_{12}BrNO_2$	5.43	5.31	30.96	30.71
m-Toloxy	81–83	90	$C_{11}H_{14}BrNO_2$	5.15	4.78	29.37	29.06
2,5-Dimethylphenoxy	99–101	94	$C_{12}H_{16}BrNO_2$	4.90	4.82	27.93	27.99
Thymoxy	56–58	43	$C_{14}H_{20}BrNO_2$	4.46	4.47	25.43	25.47
Carvacryloxy	83–84	68	$C_{14}H_{20}BrNO_2$	4.46	4.74	25.43	25.54
p-Chlorothymoxy[a]	72–74	83	$C_{14}H_{19}BrClNO_2$	4.02	3.82		
2,4-Dichlorophenoxy[b]	115–117	89	$C_{10}H_{10}BrCl_2NO_2$	4.28	4.60		

[a] Calc'd: C, 48.22; H, 5.49. Found: C, 48.53; H, 5.61. [b] Calc'd: C, 36.72; H, 3.08. Found: C, 37.16; H, 3.36.

TABLE III

3-BROMOPROPYLARYLOXYACETAMIDES $ArOCH_2CONH(CH_2)_3Br$

ArO	M.P., °C.	YIELD, %	FORMULA	ANALYSIS			
				N		Br	
				Calc'd	Found	Calc'd	Found
Phenoxy	67–69	75	$C_{11}H_{14}BrNO_2$	5.15	5.19	29.37	29.77
m-Toloxy	61–63	80	$C_{12}H_{16}BrNO_2$	4.90	4.66	27.93	27.82
2,5-Dimethylphenoxy	85.5–87.5	79	$C_{13}H_{18}BrNO_2$	4.67	5.08	26.62	26.56
Thymoxy	62–64	64	$C_{15}H_{22}BrNO_2$	4.27	4.20	24.35	24.29
Carvacryloxy	oil	73	$C_{15}H_{22}BrNO_2$	4.27	3.95	24.35	24.05
p-Chlorothymoxy[a]	66–68	81	$C_{15}H_{21}BrClNO_2$	3.86	3.85		
2,4-Dichlorophenoxy[b]	89–91	82	$C_{11}H_{12}BrCl_2NO_2$	4.11	3.84		

[a] Calc'd: C, 49.67; H, 5.84. Found: C, 50.13; H, 5.81. [b] Calc'd: C, 38.74; H, 3.55. Found: C, 38.98; H, 3.68.

TABLE IV

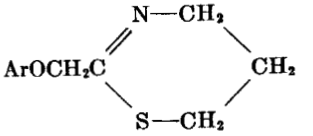
2-(ARYLOXYMETHYL)THIAZOLINES $ArOCH_2C$(=N—CH_2—S—CH_2)

ArO	PICRATES							HYDROCHLORIDES			
	M.P., °C. (dec.)	Procedure and Yield	Formula	ANALYSIS N Calc'd	N Found	S Calc'd	S Found	M. p., °C.[a]	Formula	Analysis[b] Cl Calc'd	Cl Found
Phenoxy	177–179	A (20 min., 110°), 32%; B, 9%; C, 8%	$C_{16}H_{14}N_4O_8S$	13.27	13.11	7.59	7.95	147–149	$C_{10}H_{12}ClNOS$	15.43	15.34
o-Toloxy	166–168	A (5 min., 160°), 30%	$C_{17}H_{16}N_4O_8S$	12.84	13.33	7.35	7.59	160–163	$C_{11}H_{14}ClNOS$	14.55	14.01
m-Toloxy	188–190	B, 36%	$C_{17}H_{16}N_4O_8S$	12.84	12.73	7.35	7.49	158–160	$C_{11}H_{14}ClNOS$	14.55	14.71
p-Toloxy	174–176	A (8 min., 140°), 49%	$C_{17}H_{16}N_4O_8S$	12.84	12.98	7.35	6.83	165–168	$C_{11}H_{14}ClNOS$	14.55	14.85
2,5-Dimethylphenoxy	176–178	A (5 min., 160°), 26%; B, 24%	$C_{18}H_{18}N_4O_8S$	12.44	11.88	7.12	7.27	176–180	$C_{12}H_{16}ClNOS$	13.76	13.95
o-Isopropylphenoxy	165–167	A (15 min., 130°), 25%	$C_{19}H_{20}N_4O_8S$	12.06	12.25	6.90	7.17	180–181	$C_{13}H_{18}ClNOS$	13.05	13.19
Thymoxy	167–168	A (20 min., 140°), 42%; B, 8%	$C_{20}H_{22}N_4O_8S$	11.71	11.28	6.70	7.16	149–151	$C_{14}H_{20}ClNOS$	12.41	12.45
Carvacryloxy	167–169	A (10 min., 150°), 20%; B, 9%	$C_{20}H_{22}N_4O_8S$	11.71	11.75	6.70	6.96				
m-Chlorophenoxy	185–187	A (15 min., 135°), 63%	$C_{16}H_{13}ClN_4O_8S$	12.27	12.65	7.02	6.89	172–174	$C_{10}H_{11}ClNOS$	26.84	26.43
p-Chlorophenoxy	168–169	A (20 min., 140°), 32%	$C_{16}H_{13}ClN_4O_8S$	12.27	12.28	7.02	6.69	179–181	$C_{10}H_{11}ClNOS$	26.84	26.26
2,4-Dichlorophenoxy	185–187	B, 20%	$C_{16}H_{12}Cl_2N_4O_8S$	11.40	11.80	6.53	6.64				
p-Diphenyloxy	183–185	A (10 min., 160°), 43%	$C_{22}H_{18}N_4O_8S$	11.24	10.99	6.43	6.71	150–154	$C_{16}H_{16}ClNOS$	11.60	11.99

[a] All melting points were determined in sealed capillaries. [b] These values were obtained by combustion analyses, since many of the compounds appear to give soluble complexes with silver nitrate or mercuric nitrate.

TABLE V

2-(ARYLOXYMETHYL)PENTHIAZOLINES



ArO	PICRATES							HYDROCHLORIDES			
	M.p., °C. (dec.)	Procedure and Yield	Formula	ANALYSIS N Calc'd	ANALYSIS N Found	ANALYSIS S Calc'd	ANALYSIS S Found	M.p., °C.	Formula	Analysis Cl Calc'd	Analysis Cl Found
Phenoxy	177–179	A (10 min., 170°), 58%; B, 37%; C, 10%	$C_{17}H_{16}N_4O_8S$	12.84	12.65	7.35	6.79	162–164	$C_{11}H_{14}ClNOS$	14.55[a]	14.73
o-Toloxy	158–160	A (5 min., 160°), 69%	$C_{18}H_{18}N_4O_8S$	12.44	12.62	7.12	7.46	186–187	$C_{12}H_{16}ClNOS$	13.75[a]	13.93
m-Toloxy	168–170	B, 48%	$C_{18}H_{18}N_4O_8S$	12.44	12.07	7.12	7.31	146–147	$C_{12}H_{16}ClNOS$	13.75	13.72
p-Toloxy	151–153	A (10 min., 150°), 64%	$C_{18}H_{18}N_4O_8S$	12.44	12.53	7.12	7.06	175–177	$C_{12}H_{16}ClNOS$	13.75	14.16
2,5-Dimethylphenoxy	175–176	A (5 min., 160°), 67%; B, 51%	$C_{19}H_{20}N_4O_8S$	12.07	11.61	6.90	7.13	172–173	$C_{13}H_{18}ClNOS$	13.05[a]	13.39
o-Isopropylphenoxy	155–157	A (20 min., 135°), 62%	$C_{20}H_{22}N_4O_8S$	11.71	12.06	6.70	7.12	193–195	$C_{14}H_{20}ClNOS$	12.40	12.20
Thymoxy	183–185	A (10 min., 140°), 68%; B, 64%	$C_{21}H_{24}N_4O_8S$	11.38	11.45	6.51	6.02	166–170	$C_{15}H_{22}ClNOS$	11.82[a]	12.08
Carvacryloxy	167–169	A (15 min., 120°), 20%; B, 52%	$C_{21}H_{24}N_4O_8S$	11.38	11.01	6.51	6.38	102–106	$C_{15}H_{22}ClNOS$	11.82	12.25
m-Chlorophenoxy	180–181	A (15 min., 130°), 54%	$C_{17}H_{15}ClN_4O_8S$	11.90	12.08	6.81	7.14	148–150	$C_{11}H_{13}Cl_2NOS$	12.74[a]	13.07
p-Chlorophenoxy	179–180	A (10 min., 160°), 57%	$C_{17}H_{15}ClN_4O_8S$	11.90	12.33	6.81	7.09	205–207	$C_{11}H_{13}Cl_2NOS$	25.49	25.33
2,4-Dichlorophenoxy	191–192	B, 40%	$C_{17}H_{14}Cl_2N_4O_8S$	11.09	11.29	6.35	6.65	166–168	$C_{11}H_{12}Cl_3NOS$	34.02	33.79
p-Chlorothymoxy	191–193	B, 57%	$C_{21}H_{23}ClN_4O_8S$	10.63	11.14	6.08	5.70	180–181	$C_{15}H_{21}Cl_2NOS$	10.61[a]	11.08
p-Diphenyloxy	174–176	A (10 min., 160°), 84%	$C_{23}H_{20}N_4O_8S$	10.93	10.50	6.26	6.48	189–190	$C_{17}H_{18}ClNOS$	11.09[a]	11.47

[a] These analyses were determined by titration with mercuric nitrate, while the remaining ones were carried out by combustion.

toluene solution with phosphorus pentasulfide by a modification of Salomon's synthesis (7). In a few instances [*e.g.*, 2-(carvacryloxymethyl)penthiazoline] this method was superior to A. The required amides were prepared (8) *via* the corresponding aryloxyacetyl chlorides (VI).

$$\underset{\text{VI}}{ArOCH_2COCl} \longrightarrow \underset{\substack{\text{VII } n = 2\\ \text{VIII } n = 3}}{ArOCH_2CONH(CH_2)_nBr} \xrightarrow{P_2S_5} \text{II or III.}$$

METHOD C

$$\underset{\text{V}}{ArOCH_2CSNH_2} + \underset{\substack{n = 2 \text{ or } 3\\ X = Br, Cl}}{Br(CH_2)_nX} \longrightarrow \text{II or III}$$

The synthesis was first published by Gabriel (9) and proved to be inferior to the other methods (A and B) when tested with phenoxyacetothioamide.

EXPERIMENTAL[2]

Aryloxyacetothioamides (V). The following procedure (3) gave excellent results: Ammonia was passed through 20 cc. of methanol in a pressure bottle cooled in ice, until 2 g. had been absorbed, followed by hydrogen sulfide until an additional gain in weight of 4 g. was observed. Four grams of aryloxyacetonitrile (IV) (1) was added, the bottle closed and then heated at 70–80° for one hour. The thioamides usually crystallized on cooling, but water was added in every instance to ensure complete precipitation of the product. Recrystallization was effected from ethanol. The physical constants and yields are summarized in Table I.

2-Bromoethylaryloxyacetamides (VII). Essentially the method of Leffler and Adams (8) for benzamides was used, a typical example being described below. The physical constants of the various derivatives are given in Table II.

A solution of 10.2 g. (0.05 mole) of 2-bromoethylamine hydrobromide in 75 cc. of water was placed in a flask equipped with a dropping-funnel and an efficient Hershberg stirrer, and cooled to 15° with running water. A solution of 0.055 mole of the aryloxyacetyl chloride [prepared from the corresponding acid with thionyl chloride in the absence of a solvent (10)] in 25 cc. of benzene was added, the stirrer was started, and 4.6 g. (0.115 mole) of sodium hydroxide in 95 cc. of water was dropped in over a period of five minutes. After stirring for one hour at 15° and an additional hour at room temperature, ether was added, the organic layer was washed with sodium carbonate and water, dried and evaporated. The crystalline residue was triturated with hexane and filtered. The material thus obtained was usually of nearly analytical purity.

3-Bromopropylaryloxyacetamides (VIII). These were prepared exactly as above except that 10.95 g. (0.05 mole) of 3-bromopropylamine hydrobromide was used. The pertinent information regarding these compounds is given in Table III.

2-(Aryloxymethyl)thiazolines (II) and penthiazolines (III). Method A. The optimum conditions for the fusion of 0.03 mole of thioamide and 0.025 mole of bromoalkylamine hydrobromide (without solvent) had to be determined for each case and are listed in the appropriate columns in Tables IV and V. With few exceptions (*e.g.*, the 2-diphenyloxymethyl derivatives, where the melt was directly dissolved in ethanol and picric acid added), the mixture

[2] All melting points are corrected. The microanalyses were carried out by Mr. George L. Stragand, Microchemical Laboratory, University of Pittsburgh. Thanks are due to the Misses Edwina Leathem and Frances Hoffmann for technical assistance.

was partitioned between ether and hydrochloric acid, the latter made alkaline with ammonia and re-extracted. In particularly dark colored runs, this procedure was repeated. The desired product was always crystallized as the picrate from ethanol solution.

Method B. Salomon's synthesis (7), which involved melting an amide with phosphorus pentasulfide, was improved by the introduction of toluene as solvent. The reaction was carried out by refluxing 0.002 mole of bromoalkyl aryloxyacetamide (VII or VIII) with 90 mg. of phosphorus pentasulfide in 10–15 cc. of dry toluene for four hours. After dilution with ether, the product was isolated as in A.

Preparation of hydrochlorides. The picrates were converted into the free bases using lithium hydroxide (11) and either ether or chloroform. The heterocyclic amine was dissolved in anhydrous ether (the solution filtered if necessary) and treated with the calculated amount of 7 *N* ethanolic hydrogen chloride, whereupon the hydrochlorides precipitated. None of the samples were recrystallized in order to avoid any possible ring opening (7). The melting points and analyses are reported in Tables IV and V.

SUMMARY

A series of 2-(aryloxymethyl)thiazolines and penthiazolines have been synthesized by (A) fusion of the appropriate thioamide with a bromoalkylamine hydrobromide or (B) reaction of a bromoalkyl aryloxyacetamide with phosphorus pentasulfide.

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