[CONTRIBUTION FROM THE WARNER INSTITUTE FOR THERAPEUTIC RESEARCH]

Phenoxy- and Benzyloxyalkyl Thiocyanates[1]

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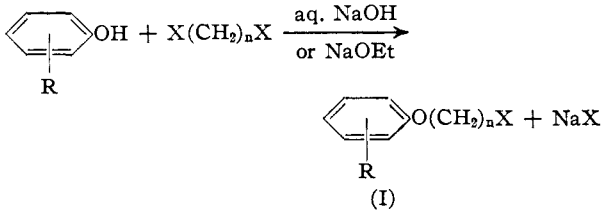
A series of phenoxy- and benzyloxyalkyl thiocyanates has been prepared for pharmacological evaluation as fungicides against pathogenic fungi associated with dermatophytosis.

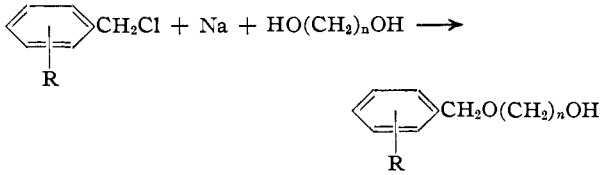
Compounds of the type herein described have been studied in the past almost exclusively with respect to their insecticidal properties[2-5] and only in isolated cases has any mention been made of their anti-fungal activity.[6] In contrast, the activity of alkyl and aryl thiocyanates and isothiocyanates as fungicides as well as insecticides is fairly well known[6,7] and this was further verified by the testing of certain known as well as new aryl isothiocyanates prepared in this Laboratory.[8] A consideration of the aforementioned facts, coupled with the results obtained from the fungicidal screening of certain alkoxyalkyl thiocyanates previously described in the literature, prompted the present investigation.

The thiocyanates (Tables IV and V) were prepared, by metathesis with KSCN, from the corresponding halides. The halides in the phenoxy series (Table I) were prepared from the appropriately substituted phenol either by reaction of the latter with an alkylene halide in the presence of sodium hydroxide in an aqueous medium,[9] or by the action of the alkylene halide on the sodium salt of the phenol in an anhydrous alcoholic medium. The low yields of (I) are attributed to the formation of the diether.



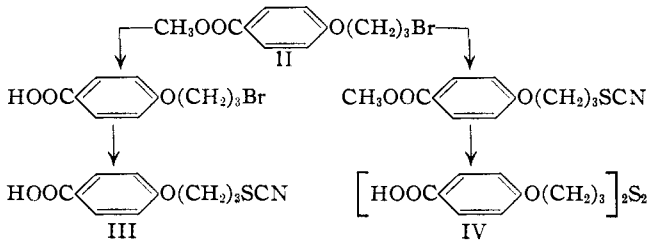
(I)

In the benzyloxy series, the halides (Table III) were prepared from the corresponding alcohols by treatment with thionyl chloride in the presence of a tertiary amine and chloroform. The alcohols (Table II) were easily obtained by refluxing the appropriate benzyl halides with sodium and a polymethylene glycol in the presence of xylene.



The reaction of the halides with KSCN proceeded quite readily when bromides were used, whereas chlorides proved considerably less satisfactory. In many cases, copper or KI was used to catalyze the latter reaction.

The structural configuration of the thiocyanates has not been intensively studied and the possibility exists that some of these compounds rearrange to the isothiocyanate during distillation. It has been shown that thiocyanates yield disulfides when hydrolyzed with acids or bases,[10] or when heated with tertiary amines in acetic acid.[11] γ-(*p*-Bromophenoxy)-propyl thiocyanate, when subjected to alkaline hydrolysis, was shown to yield



the corresponding disulfide, thereby establishing the thiocyanate structure. Similarly, a study of the preparation of *p*-(γ-thiocyanopropoxy)-benzoic acid (III) from methyl *p*-(γ-bromopropoxy)-benzoate (II) indicated the necessity of saponification of the carbomethoxy group with alcoholic KOH previous to reaction with KSCN. The reverse procedure led to the formation of the disulfide (IV) thereby establishing (III) as a thiocyanate and not an isothiocyanate.

The yields reported in a majority of the preparations are on the basis of single experiments and do not necessarily constitute the maximum yield obtainable.

The pharmacological evaluation of the compounds herein described will be reported elsewhere by other workers.[12]

Experimental

The following examples are illustrative of the method of preparation of the compounds listed in the tables. All melting and boiling points are uncorrected.

Procedure I, γ-(*o*-Isopropylphenoxy)-propyl Bromide (Table I, Compound 25).—Twenty-three grams (1 mole) of metallic sodium was dissolved in 450 ml. of absolute alcohol with stirring. To this solution was added 136 g. (1 mole) *o*-isopropylphenol and then 250 g. (25% excess) of trimethylene bromide at a moderate rate. Inorganic salt started separating a few minutes after addition of the bromide. The mixture was refluxed for 5 hours, cooled and filtered. There was a quantitative recovery of sodium bromide. The alcohol was distilled and the unreacted bromide removed at 12–15 mm. Then the residue was fractionated

(1) Presented before the Division of Medicinal Chemistry at the 119th meeting of the A.C.S., Cleveland, Ohio, April, 1951.

(2) G. H. Coleman, U. S. Patents 2,185,183, 2,185,184, 2,185,185 (Jan. 2, 1940).

(3) J. E. Livak, U. S. Patents 2,185,207 and 2,185,208 (Jan. 2, 1940).

(4) A. Hartzell and F. Wilcoxon, *Contrib. Boyce Thompson Inst.*, **6**, 269 (1934).

(5) E. K. Harvill and J. M. Arthur, *ibid.*, **13**, 79 (1943).

(6) F. Wilcoxon and S. A. E. McCallen, *ibid.*, **7**, 333 (1935).

(7) W. H. Davies and W. A. Sexton, *Biochem. J.*, **40**, 331 (1946).

(8) F. H. McMillan and J. A. King, THIS JOURNAL, **72**, 4323 (1950).

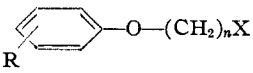
(9) C. S. Marvel and A. L. Tanenbaum, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 435.

(10) C. Rabaut, *Bull. soc. chim.*, **27**, 690 (1902).

(11) E. Hoggarth and W. A. Sexton, *J. Chem. Soc.*, 815 (1947).

(12) L. Landís, D. Kley and N. Ercoli, *J. Am. Pharm. Assoc., Sci. Ed.*, scheduled for publication, June, 1951.

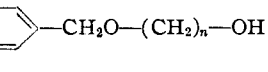
TABLE I

PHENOXYALKYL HALIDES 

No.	R	n	X	B.p. °C.	Mm.	$n^{20}D$	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Halogen Calcd.	Halogen Found	Yield, %	Procedure
1		4	Cl	150	0.2	1.5215		$C_{10}H_{13}OCl$							21[a]	1
2		5	Cl	116	1.3	1.5144		$C_{11}H_{15}OCl$							16[b]	1
3	2-Br	2	Br	116	0.2			$C_8H_8OBr_2$							63[c]	2
4	4-Br	2	Br				57	$C_8H_8OBr_2$							44[d]	2
5	2-Cl	2	Br	136	5	1.569		C_8H_8OClBr							40[e]	2
6	3-Cl	2	Br	85	0.1	1.5680		C_8H_8OClBr	40.76	40.78	3.40	3.12	49.04	48.83	23	2
7	4-Cl	2	Br	108	1		68	C_8H_8OClBr	40.76	41.10	3.40	3.73	49.04	48.60	26	2
8	2-CH_3	2	Br	100	0.6	1.5479		$C_9H_{11}OBr$							52[f]	2
9	3-CH_3	2	Br	80	1.1	1.5472		$C_9H_{11}OBr$							54[g]	2
10	4-CH_3	2	Br	110	1		49	$C_9H_{11}OBr$							33[h]	2
11	4-Br	3	Br	150	0.7	1.5792	50	$C_9H_{10}OBr_2$							53[i]	2
12	2-Cl	3	Br	120	0.5	1.5590		$C_9H_{10}OClBr$	43.29	43.55	4.00	4.07	46.29	45.71	44	2
13	3-Cl	3	Br	108	1	1.5580		$C_9H_{10}OClBr$	43.29	43.39	4.00	3.97	46.29	45.60	31	2
14	4-Cl	3	Br				37	$C_9H_{10}OClBr$	43.29	43.28	4.00	4.18	46.29	46.33	[j]	2
15	3-CH_3	3	Br	120	2	1.5422		$C_{10}H_{13}OBr$	52.40	52.60	5.68	5.51	34.90	34.99	10	2
16	4-Br	4	Cl	128	0.03	1.5548		$C_{10}H_{12}OClBr$	45.54	45.66	4.55	4.61	43.83	44.06	38	2
17	2-Cl	4	Cl	130	2	1.5350		$C_{10}H_{12}OCl_2$	54.79	55.02	5.47	5.50	32.42	32.11	59	2
18	3-Cl	4	Cl	114	0.4	1.5345		$C_{10}H_{12}OCl_2$	54.79	54.54	5.47	5.57	32.42	32.40	48	2
19	2-CH_3	4	Cl	114	1.5	1.5189		$C_{11}H_{15}OCl$	66.50	66.82	7.56	7.42	17.88	17.55	26	1
20	3-CH_3	4	Cl	93	0.1	1.5199		$C_{11}H_{15}OCl$	66.50	66.53	7.56	7.60	17.88	17.79	45	1
21	4-CH_3	4	Cl	97	.2	1.5180		$C_{11}H_{15}OCl$	66.50	66.43	7.56	7.36	17.88	17.73	20	3
22	4-NO_2	3	Br	155	.1			$C_9H_{10}O_3NBr$							35[k]	3
23	4-OCH_3	2	Br	95–104	.3			$C_{10}H_{11}O_2Br$							14[l]	1
24	2-$CH(CH_3)_2$	2	Br	80	.04	1.5329[t]		$C_{11}H_{15}OBr$							19[m]	2
25	2-$CH(CH_3)_2$	3	Br	84	.1			$C_{12}H_{17}OBr$							35[n]	1
26	3,4-$>CH(CH_3)_2$	2	Br	90	.3			$C_{11}H_{15}OBr$	54.32	55.32	6.17	6.22			21	2
27	2-$COOCH_3$	3	Br	150–155	1.4			$C_{11}H_{13}O_3Br$							37[o]	1
28	4-$COOCH_3$	3	Br	164	1.5			$C_{11}H_{13}O_3Br$							29[o]	1
29	2-$COOCH_3$	3	Cl	140	1.2			$C_{11}H_{13}O_3Cl$							37[o]	1
30	4-$COOCH_3$	3	Cl	163	3.2			$C_{11}H_{13}O_3Cl$							40[o]	1
31	2-COOH	3	Br				71	$C_{10}H_{11}O_3Br$	46.33	46.59	4.25	4.35	30.89	31.00	[p,q]	4
32	4-COOH	3	Br				161	$C_{10}H_{11}O_3Br$	46.33	47.29	4.25	4.68	30.89	30.95	[p]	4
33	2-COOH	3	Cl				75	$C_{10}H_{11}O_3Cl$	55.94	56.58	5.13	5.43	16.55	16.74	[p,r]	4
34	4-COOH	3	Cl				156–157	$C_{10}H_{11}O_3Cl$	55.94	55.52	5.13	5.03	16.55	16.73	[p,s]	4

[a] J. v. Braun and E. Beschke, *Ber.*, **39**, 4357 (1906), report the preparation and analysis of this compound, b.p. 147° (12 mm.). [b] J. v. Braun and A. Steindorff, *ibid.*, **38**, 962 (1905), report preparation and analysis, b.p. 155° (15 mm.). [c] Reported and analyzed by R. Stoermer and M. Schaffer, *ibid.*, **36**, 2874 (1903), b.p. 160–162° (16 mm.). [d] B. Jones, *J. Chem. Soc.*, 1831 (1935), reports m.p. 58°. [e] R. Stoermer and M. Schaffer, reference *c*, prepared and analyzed this compound, b.p. 140–142° (13 mm.). [f] R. Rindfusz, P. M. Ginnings and V. Harnack, THIS JOURNAL, **42**, 157 (1920), prepared and analyzed this compound and reported b.p. 133–134° (20 mm.), $n^{27}D$ 1.544. [g] W. A. Jacobs and M. Heidelberger, *J. Biol. Chem.*, **21**, 440 (1915), prepared and analyzed this compound, b.p. 136–137° (14 mm.). [h] L. Gattermann, *Ann.*, **357**, 356 (1907), prepared and analyzed this compound, b.p. 254–255°, m.p. 40°. [i] B. Jones, *J. Chem. Soc.*, 1831 (1935), reports b.p. 169° (12 mm.), m.p. 49.5°. [j] Recrystallized from ethanol; poor yield. [k] Solidifies at room temperature; used crude in reaction with KSCN; unreacted phenol was washed out with NaOH solution before distilling; decomposition occurs if distilled through a column. [l] E. Kahane and J. Levy, *Bull. soc. chim. biol.*, **27**, 562 (1945), b.p. 154° (11 mm.). Worked up in same manner as $-NO_2$ compound. [m] W. S. Gump and E. Nikawitz, THIS JOURNAL, **72**, 3847 (1950), b.p. 123–127° (5 mm.), $n^{20}D$ 1.535 [n] Distilled through 1-foot glass helices packed column; no analytical sample; used slightly impure in reaction with KSCN. [o] Distilled through 1-foot glass helices packed column; used slightly impure in subsequent saponification. [p] Yields from corresponding esters are quantitative. [q] Recrystallized from Skellysolve B–ether mixture. [r] Recrystallized from methanol–water (2:1). [s] Recrystallized from 80% ethanol. [t] nD at 25°.

TABLE II

BENZYLOXYALKANOLS 

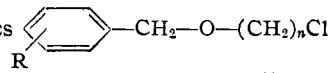
No.	R	n	B.p. °C.	Mm.	$n^{20}D$	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Yield, %	Procedure
1		2	95	0.25	1.5209	$C_9H_{12}O_2$							81[a,c]	5
2		3	114	.9	1.5184	$C_{10}H_{14}O_2$							60[b]	5
3		5	140	.4	1.5099	$C_{12}H_{18}O_2$	74.22	74.36	9.27	9.05			35	5
4	2-Cl	2	84	.03	1.5348	$C_9H_{11}O_2Cl$	57.90	58.05	5.89	5.87	19.00	18.95	84	5
5	2-Cl	3	94	.5	1.5245	$C_{10}H_{13}O_2Cl$	59.85	59.82	6.53	6.80	17.70	17.55	28	5
6	2-Cl	5	139	.5	1.5202	$C_{12}H_{17}O_2Cl$	63.02	63.16	7.44	7.74	15.54	15.65	54	5

[a] G. Bennett, *J. Chem. Soc.*, **127**, 1277 (1925) prepared and analyzed this compound, b.p. 138° (15 mm.). [b] G. Bennett and A. L. Hock, *ibid.*, 472 (1927) prepared and analyzed this compound. b.p. 155° (23 mm.), 172° (43 mm.). [c] The corresponding thenoxy compound was also prepared, b.p. 70–73° (0.05 mm.). *Anal.* Calcd. for $C_7H_{10}O_2S$: C, 53.16; H, 6.33; S, 20.25. Found: C, 52.95; H, 6.63; S, 20.41.

in vacuo. (This material was not absolutely pure but was used as such in reaction with KSCN.)

Methyl *p*-(γ-Bromopropoxy)-benzoate (Table I, Compound 28).—Forty-six grams (2 moles) of metallic sodium was dissolved in 700 ml. of absolute ethanol. To this was added with stirring 305 g. (2 moles) of methyl *p*-hydroxybenzoate in 500 ml. of absolute ethanol. There was then added 500 g. (25% excess) of trimethylene bromide and the

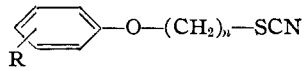
TABLE III

BENZYLOXYALKYL HALIDES 

No.	R	n	B.p. °C.	B.p. Mm.	$n^{20}D$	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Chlorine Calcd.	Chlorine Found	Yield, %	Procedure
1		2	75	0.2	1.5181	$C_9H_{11}OCl$							77[a,e]	6
2		3	88	.5	1.5113	$C_{10}H_{13}OCl$							65[b]	6
3		4	75	.07	1.5109	$C_{11}H_{15}OCl$							13[c]	[d]
4		5	86	.01	1.5079	$C_{12}H_{17}OCl$	67.76	67.86	8.00	7.82	16.70	16.57	75	6
5	2-Cl	2	72	.01	1.5339	$C_9H_{10}OCl_2$	52.69	52.47	4.88	5.15	34.63	34.83	77	6
6	2-Cl	3	120	.1	1.5268	$C_{10}H_{12}OCl_2$	54.79	54.83	5.47	5.38	32.42	32.35	48	6
7	2-Cl	5	144	1.6	1.5193	$C_{12}H_{16}OCl_2$	58.30	58.34	6.48	7.62	28.74	28.99	7	6

[a] G. Bennett, *J. Chem. Soc.*, **127**, 1277 (1925), prepared and analyzed this compound, b.p. 124° (20 mm.), $n^{20}D$ 1.5204. [b] G. Bennett and A. Hock, *ibid.*, 472 (1927), prepared and analyzed this compound, b.p. 129° (16 mm.). [c] *Idem.*, report b.p. 135° (12 mm.). [d] Prepared from benzyl alcohol, metallic sodium and 1,4-dichlorobutane by refluxing for 30 minutes, filtering and fractionally distilling. [e] The corresponding thenoxy compound was also prepared, b.p. 69–70° (0.1 mm.). *Anal.* Calcd. for C_7H_9OClS: C, 47.59; H, 5.14. Found: C, 47.66; H, 5.09.

TABLE IV

PHENOXYALKYL THIOCYANATES 

No.	R	n	B.p. °C.	B.p. Mm.	$n^{20}D$	M.p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Yield, %	Procedure
1		2	152	0.4	1.5599		C_9H_9ONS							81[a]	7
2		3	125	.4	1.5518		$C_{10}H_{11}ONS$							83[b]	7
3		4	155	.1	1.5480	38–39	$C_{11}H_{13}ONS$	63.77	63.82	6.28	6.07	6.76	6.79	37[c,o]	7b
4	4-Br	2				62–63	C_9H_8ONBrS	41.87	42.17	3.10	3.08	5.42	5.17	51[d,e]	7
5	2-Cl	2	180	3.0		37–39	C_9H_8ONClS	50.59	50.48	3.75	3.47	6.56	6.67	83	7
6	3-Cl	2	126	0.1			C_9H_8ONClS	50.59	50.42	3.75	3.68	6.56	6.33	33	7
7	4-Cl	2	137	.1	1.5710		C_9H_8ONClS	50.59	50.77	3.75	3.92	6.56	6.44	17	7
8	2-CH_3	2	132	.3			$C_{10}H_{11}ONS$	62.17	62.03	5.70	5.54	7.25	7.09	60[f,g]	7
9	3-CH_3	2	158	4.0	1.5534		$C_{10}H_{11}ONS$	62.17	62.19	5.70	5.89	7.25	7.42	63[f]	7
10	4-CH_3	2	130	0.5	1.5530		$C_{10}H_{11}ONS$	62.17	61.88	5.70	6.02	7.25	7.24	66[f,p]	7
11	4-Br	3				48–49	$C_{10}H_{10}ONBrS$	44.11	44.49	3.68	3.68	5.15	5.21	53	7, 7a
12	2-Cl	3	165	1.3	1.5644		$C_{10}H_{10}ONClS$	52.75	52.90	4.39	4.52	6.15	6.22	52	7
13	3-Cl	3	164	1.2	1.5624		$C_{10}H_{10}ONClS$	52.75	52.67	4.39	4.13	6.15	6.12	96[h]	7
14	4-Cl	3	50	0.5			$C_{10}H_{10}ONClS$	52.75	52.43	4.39	4.37	6.15	5.84	40	7
15	3-CH_3	3	138	.6	1.5471		$C_{11}H_{13}ONS$	63.77	63.73	6.28	6.31	6.76	6.89	42	7
16	4-Br	4	180	.5	1.5410		$C_{11}H_{12}ONBrS$	46.15	45.95	4.20	4.07	4.89	4.97	66[i]	7b
17	3-Cl	4	186	1.9	1.5543		$C_{11}H_{12}ONClS$	54.65	54.62	4.97	5.02	5.80	5.72	55[m,i]	7b
18	2-CH_3	4	138	0.1	1.5533		$C_{12}H_{15}ONS$	65.16	65.15	6.79	6.37	6.33	6.21	15[n]	7b
19	4-CH_3	4	193	5.0	1.5410		$C_{12}H_{15}ONS$	65.16	65.35	6.79	6.88	6.33	6.07	27[q]	7b
20	2-COOH	3				69–70	$C_{11}H_{11}O_3NS$	55.69	55.73	4.64	4.64	5.94	6.05	35[i]	7
21	4-COOH	3				159	$C_{11}H_{11}O_3NS$	55.69	55.65	4.64	4.71	5.94	5.92	35	7
22	4-NO_2	3				53–54	$C_{10}H_9O_3N_2S$	50.42	50.51	4.20	4.02	11.76	11.78	44	7
23	4-OCH_3	2	141	0.4			$C_{10}H_{11}O_2NS$	57.42	57.42	5.31	5.03	6.69	6.81	43	7
24	2-$CH(CH_3)_2$	2	123	.3	1.5402[j]		$C_{12}H_{15}ONS$	65.16	65.30	6.79	7.16	6.33	6.45	47	7, 7a
25	3,4-$CH(CH_3)_2$	2	130	.3			$C_{12}H_{15}ONS$	65.16	65.32	6.79	6.77	6.33	6.39	51	7
26	2-$CH(CH_3)_2$	3	140	.1	1.5363[k]		$C_{13}H_{17}ONS$	66.34	66.13	7.28	7.18	5.97	6.00	60	7, 7a
27	2-Br	2	162	1.7	1.5920		C_9H_8ONBrS	41.87	41.62	3.10	3.34	5.42	5.33	51	7
28	2-Cl	4	164	0.5	1.5544		$C_{11}H_{12}ONClS$	54.65	54.87	4.97	4.98	5.80	5.64	40	8

[a] Reference 4, m.p. 21°. [b] Reference 4, b.p. 188–191° (14 mm.). [c] Recrystallized from methanol. [d] Recrystallized from methanol. [e] *Anal.* Calcd. for C_9H_8ONBrS: Br, 30.96. Found: Br, 31.29. [f] These compounds were used by Harvill and Arthur, reference 5, in testing as insecticides but their method of preparation is only generically mentioned. No analyses or physical constants were mentioned. [g] Solidifies at room temperature. [h] *Anal.* Calcd. for $C_{10}H_{10}ONClS$: Cl, 15.58. Found: Cl, 15.65. [i] Recrystallized from benzene-Skellysolve B–ether. [j] n_D at 27°. [k] n_D at 27°. [l] Refluxed 24 hours without KI. [m] Refluxed 18.5 hours without KI. [n] Refluxed 12 hours without KI. [o] Refluxed 75 hours without KI. [p] Von H. P. Vogelsang, Th. Wagner-Jauregg and R. Rebling, *Ann.*, **569**, 187 (1950), report b.p. 181–184° (0.9 mm.), $n^{15.5}D$ 1.5615. [q] *Idem.*, b.p. 190–193° (0.15 mm.), $n^{17}D$ 1.5491.

mixture worked up the same as above (used as such in subsequent saponification).

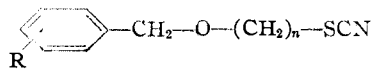
Procedure II. δ-(*p*-Toloxy)-butyl Chloride (Table I, Compound 21).—Prepared according to reference 9 from *p*-cresol, 1,4-dichlorobutane and aqueous sodium hydroxide.

γ-(*p*-Bromophenoxy)-propyl Bromide (Table I, Compound 11).—Prepared according to reference 9. The material solidified and was recrystallized from ethanol. In reactions carried out by this method it was found that the rate of addition of the sodium hydroxide did not appreciably affect the yield.

Procedure III. γ-(*p*-Nitrophenoxy)-propyl Bromide (Table I, Compound 22).—Twenty-three grams (1 mole) of metallic sodium was dissolved in 300 ml. of absolute ethanol (stirring and slight heat were used to effect solution). To this was added 139 g. (1 mole) of *p*-nitrophenol in 250 ml. of absolute ethanol and 250 g. (25% excess) of trimethylene bromide. The mixture was refluxed for 5 hours, cooled and filtered. The alcohol was removed *in vacuo* and the residue dissolved in ether (last bit of inorganic salt separated here and was removed). The ethereal solution was extracted twice with 3 *N* sodium hydroxide and twice with water to remove unreacted phenol. The ether layer was dried over calcium chloride, filtered and the ether evaporated. Unreacted halide was distilled and the residue fractionated using only a still head. The product solidified at room temperature.

Procedure IV. *p*-(γ-Bromopropoxy)-benzoic Acid (Table I, Compound 31).—Two grams of the corresponding ester (see procedure I) was heated with a slight excess of alco-

TABLE V

BENZYLOXYLALKYL THIOCYANATES 

No.	R	n	B.p. °C.	B.p. Mm.	$n^{25}D$	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found	Yield, %	Procedure
1		3	124	0.1	1.5348	$C_{11}H_{13}ONS$	63.77	63.95	6.28	6.45	6.76	6.72	13	8
2		5	161	0.6	1.5292	$C_{13}H_{17}ONS$	66.38	66.15	7.23	7.51	5.96	5.99	47	8
3	2-Cl	2	160	1.5	1.5528	$C_{10}H_{10}ONClS$	52.75	52.85	4.39	4.74	6.15	6.36	16	8
4	2-Cl	3	152	0.8	1.5506	$C_{11}H_{12}ONClS$	54.66	54.80	4.97	5.18	5.79	5.70	18	8

holic potassium hydroxide on a steam-bath for about 5 minutes at 50°. The mixture was then poured into a large excess of cold water, resulting in a clear solution. The mixture was acidified with hydrochloric acid (1:1) and a fluffy white solid precipitated; this was filtered and recrystallized from ethanol.

Procedure V. β-(*o*-**Chlorobenzyloxy**)-**ethanol** (Table II, Compound 4).—One and six-tenths gram (0.07 mole) of metallic sodium was dissolved in 18.6 g. (0.3 mole) of ethylene glycol and to this was added 10 ml. of xylene with stirring. There was then added dropwise a solution of 20 g. (0.1 mole) of *o*-chlorobenzyl chloride in 9 ml. of dry xylene with stirring and the mixture brought to reflux and maintained there for 15 minutes. It was cooled and filtered, the precipitate washed with xylene and the xylene removed from the filtrate *in vacuo*. The residue was fractionated *in vacuo*.

Procedure VI. β-(*o*-**Chlorobenzyloxy**)-**ethyl Chloride** (Table III, Compound 5).—Into a flask previously cooled in an ice-bath was placed 7 g. (0.037 mole) of β-(*o*-chlorobenzyloxy)-ethanol (procedure V) and 4.5 g. (0.037 mole) of dimethylaniline. To this solution was slowly added a solution of 4.8 g. (0.041 mole) of thionyl chloride in 3.4 ml. of chloroform, keeping the temperature between 20–30°. The mixture was then refluxed for 30 minutes, cooled and poured into 50 ml. of dilute hydrochloric acid. The layers were separated. The upper layer was extracted twice with chloroform and the lower layer washed with dilute hydrochloric acid and water. The chloroform extracts were added to the lower layer and the chloroform removed on a steam-bath. The residue was fractionated.

Procedure VII. γ-(*p*-**Nitrophenoxy**)-**propyl Thiocyanate** (Table IV, Compound 22).—Eighty ml. of absolute ethanol, 36 g. (0.14 mole) of γ-(*p*-nitrophenoxy)-propyl bromide (procedure III) and 15 g. (10% excess) of KSCN were refluxed with stirring for 6 hours. The solution was clear at first and got turbid in about 15 minutes, when salt started separating out. It was cooled and poured into a large excess of cold water. A yellow solid separated, was filtered, and then recrystallized from ethanol.

γ-(*o*-**Isopropylphenoxy**)-**propyl Thiocyanate** (Table IV, Compound 26).—A mixture of 50 ml. of absolute alcohol, 25.6 g. (0.1 mole) of the corresponding bromide (procedure I) and 10.7 g. (10% excess) of KSCN was refluxed with stirring for 6 hours, then cooled and diluted with a large excess of water. The oil that separated was extracted with ether, the ether dried and removed and the residue distilled *in vacuo*.

p-(γ-**Thiocyanopropoxy**)-**benzoic Acid** (Table IV, Compound 21).—Two hundred and fifty ml. of alcohol, 46.5 g. of the corresponding bromide (procedure IV) and 19 g. of KSCN were refluxed for 4 hours and worked up the same as above. The solid was recrystallized from ethanol.

Procedure VIIA. γ-(*p*-**Bromophenoxy**)-**propyl Thiocyanate** (Table IV, Compound 11).—This can be prepared either from the pure bromide (procedure II) or from the crude bromide after the unreacted trimethylene bromide has been removed, calculating reagent quantities on the assumption that the crude material is 100% pure. Using pure material the reaction was carried out in the same manner as described under procedure VII. If the crude material was used, after the initial reaction and cooling the alcohol was distilled and the residue washed with sodium carbonate solution (2%) and water to remove unreacted phenol. The residual oil which solidified was recrystallized from methanol. Over-all yields based on *p*-bromophenol are comparable in the two methods. Although this method has only been applied to compounds 11, 24 and 26 it is probable that it can be applied to any of the compounds in Table IV prepared from the corresponding bromo compounds.

Procedure VIIB. δ-(*p*-**Toloxy**)-**butyl Thiocyanate** (Table IV, Compound 19).—Thirty-five ml. of alcohol, 10.9 g. (0.055 mole) of the corresponding chloride (procedure II) and 5.8 g. (0.06 mole) of KSCN were refluxed for 9 hours. Ten grams (0.06 mole) of KI was added and the mixture refluxed for an additional 7 hours, cooled, ether added and the solid filtered. The solvents were removed and the residual oil fractionated *in vacuo*.

Procedure VIII. β-(*o*-Chlorobenzyloxy)-**ethyl Thiocyanate** (Table V, Compound 3).—One hundred and fifty ml. of alcohol, 52.7 g. (0.257 mole) of the corresponding chloro compound (procedure VI), 29.9 g. (0.308 mole) of KSCN and 1 g. of copper powder were refluxed for 24 hours, cooled and the copper filtered off. Ether was added and the precipitate filtered and washed with alcohol. The solvents were removed from the filtrate and the residue fractionated *in vacuo*.

Bis-[γ-(*p*-**Bromophenoxy**)-**propyl**]**Disulfide.**—Two grams of γ-(*p*-bromophenoxy)-propyl thiocyanate was heated for 15 minutes on a steam-bath at 50° with an excess of alcoholic KOH; the solution was cooled and diluted with water. An oil separated and was extracted with ether. The ether layer was separated, dried and the ether removed. The residual oil solidified and was recrystallized from ethanol, m.p. 58–59°.

Anal. Calcd. for $C_{18}H_{20}O_2Br_2S_2$: C, 43.91; H, 4.10; Br, 32.47. Found: C, 44.22; H, 4.04; Br, 32.80.

Bis-[γ-(*p*-**Carboxyphenoxy**)-**propyl**] **Disulfide.**—Prepared from methyl *p*-(γ-thiocyanopropoxy)-benzoate by procedure IV. Recrystallized from dioxane, m.p. 234°.

Anal. Calcd. for $C_{20}H_{22}O_6S_2$: C, 56.87; H, 5.21; S, 15.2. Found: C, 56.39; H, 5.15; S, 16.8.

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