The larger, more rigid oximes, **1b** and **2a** are AChE inhibitors at the concns where they function as reactivators. 2-PAM and TMB-4 (**3a**) are effective reactivators at concns where no inhibition occurs. Whereas **1a** and **2b** are better inhibitors than **1b** and **2a** the opposite relationship is observed for TMB-4 (**3a**) and **3b**. This change may be the result of the flexibility of the chain and/or the distance separating the quaternary nitrogens. Further studies are needed to clarify the situation.

Experimental Section[6]

All melting points were determined on a Mel-Temp apparatus and are uncorrected. Nmr spectra were determined on a Varian T-60 spectrometer (DMSO-d_6) (TMS) and are expressed in ppm. The data were as expected.

***p,p'*-Bis(pyridinium-4-carbaldoximeacetyl)biphenyl Dibromide (1b) Method A.**—To a hot soln of *p,p'*-bis(bromoacetyl)-biphenyl (3.96 g, 0.01 mole) in 50 ml of THF was added a hot soln of *syn*-pyridine-4-carbaldoxime (0.022 mole) in 25 ml of THF. After boiling 5 min, the product was collected by filtration and washed several times with hot THF; yield 70%, mp 235–237° dec. *Anal.* ($C_{28}H_{24}N_4O_4Br_2$) C, H, N.

(6) Where analyses are indicated only by symbols of the elements, anal. results obtained for those elements are within ±0.4% of the theor values.

Synthesis and Pharmacological Activity of Dialkylaminoethyl Esters and Amides of Phenylmercaptoacetic Acid and Its Derivatives

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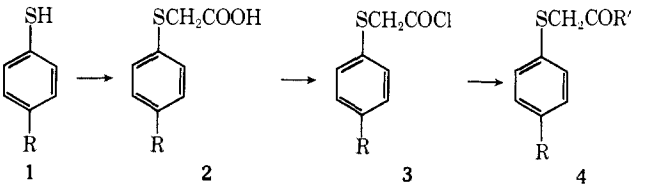
Esters and amides of phenoxyacetic acid and their derivatives[1-5] possess a wide spectrum of biol activity. The diethylaminoethylamide of *p*-chlorophenoxyacetic acid demonstrated antidepressant, analgetic, and local anesthetic properties that were comparable and in some instances greater than that of imipramine, aspirin, and lidocaine. The dimethylaminoethyl ester of *p*-chlorophenoxyacetic acid appeared to possess centrally stimulating properties. It is the first of a series of a new class of compds, the activity of which appears specifically directed toward subcortical regions of the brain.[1] A summation of the prepn and pharmacology of some isosteric compounds in this series, specifically those with S substitution of O, is presented in this paper.

Phenylmercaptan and 4-methyl and 4-chlorophenylmercaptan (**1**) were used as the starting materials for these syntheses. The corresponding acids (**2**) were readily prepd by the action of sodium chloracetate on the sodium mercaptan. Prepn of the dialkylaminoethyl esters (**4**) (Table I) was achieved by treating di-



alkylaminoethanol with the mercaptoacetyl chloride (**3**) in $CHCl_3$. Dialkylaminoethylamides of these acids were also prepd (**4**) by treating the acid chloride with the corresponding dialkylaminoethylamine in alk medium.

Experimental Section

Mp were detd in capillary tubes and are uncor. Bp are uncor. Hydrochlorides were prepd in abs EtOH or Et_2O. Oxalates were prepd by adding an equimolar propoption of oxalic acid in abs EtOH to a soln of the amine in abs EtOH. Salts were purified by recrystn from abs EtOH or from abs EtOH–anhyd Et_2O.

Phenylmercaptans (**1**).—4-Methylphenylmercaptan was prepd by redn of 4-methylphenylsulfonyl chloride with Zn and H_2SO_4 at −5 to 0°:[6] yield 96%; mp 42–43°; bp 192–194°. 4-Chlorophenylmercaptan was prepd by the same procedure: yield 97%; mp 53–55°; bp 205–206°. The phenylmercaptan was commercially available.

Phenylmercaptoacetic Acid and 4-Methyl- and 4-Chlorophenylmercaptoacetic Acid (**2**).—These compds were obtd by treating 1 mole of sodium chloracetate with 1 mole of sodium mercaptan in aq soln as previously described.[2,7]

Acid Chlorides (**3**).—These were prepd by refluxing the acid with excess $SOCl_2$. Excess $SOCl_2$ was distd off and the residue was taken up with C_6H_6 and evapd again to dryness. The crude chlorides were used as such in the next step.

Dialkylaminoethylphenylmercapto Acetates (**4**).—A soln of phenylmercaptoacetyl chloride (0.03 mole) in approx 50 ml of anhyd Et_2O was added dropwise to a stirred soln of the appropriate dialkylaminoethanol (0.03 mole) in 100 ml of $CHCl_3$. Stirring was contd for 3 min after completion of the addn, 5% HCl (100 ml) was then added, and the mixt was stirred vigorously for 10 min. The aq layer was sepd, made alk with 10% NaOH, and extd with Et_2O. The exts were washed with H_2O, dried (Na_2SO_4), and evapd. The residual oil was distd *in vacuo*.

Dialkylaminoethyl 4-methylphenylmercapto acetates and dialkylamino-4-chlorophenylmercapto acetates were obtained in a similar manner.

The oily bases were converted to the corresponding salts: oxalates (anal. samples) and hydrochlorides (pharmacol samples). Yields, bp of bases, mp of hydrochlorides and oxalates, and anal. data are given in Table I.

Dialkylaminoethylamides of Phenylmercaptoacetic Acid (**4**).—A soln of phenylmercaptoacetyl chloride (0.05 mole) in 50 ml of anhyd Et_2O was added dropwise with vigorous stirring to a mixt of the dialkylaminoethylamine (0.05 mole) in 150 ml of $CHCl_3$ and Na_2CO_3 (0.05 mole) in 50 ml of H_2O. Stirring was contd for 1 hr after completion of the addn. The $CHCl_3$ layer was sepd, washed with H_2O, dried (Na_2SO_4), and distd. The oily bases were converted to oxalates and hydrochlorides without further purification.

Dialkylaminoethylamide of 4-methylphenylmercaptoacetic acid was prepd in a similar manner (see Table I).

Pharmacology.—The iv primary mouse screen was used to characterize the gross pharmacological, toxicological, and behavioral properties of these compounds. Male, albino mice of the Swiss-Webster strain, weighing 20–25 g, were used. Each animal was observed for gross activity and overt symptoms of compd-related effects at 3, 15, 30, and 60 min, postinjection, and thereafter at periodic intervals until the effects disappeared. The combined statistical procedure of Weil and Thompson[8]

(1) G. Thuillier and P. Rumpf, *Bull. Soc. Chim. Fr.*, 1786 (1960).
(2) G. Thuillier, S. Marlier, B. Saville, and P. Rumpf, *ibid.*, 1084 (1963).
(3) G. Thuillier, J.-Marie DuPont, A. Vilar, and P. Rumpf, *ibid.*, 1087 (1963).
(4) G. Thuillier, *Chim. Ther.*, **1**, 82 (1966).
(5) W. v. Staehr and K. Karzel, *ibid.*, **1**, 444 (1966).
(6) A. Vogel, "Textbook of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., London, 1956, pp 822, 827.
(7) P. Friedlander and A. Chwala, *Monatsh. Chem.*, **28**, 273 (1907).
(8) J. Thompson, *Bacteriol. Rev.*, **11**, 115 (1947); T. Weil, *Biometrics*, **8**, 51 (1952).

TABLE I
DIALKYLAMINOETHYL ESTERS AND AMIDES OF PHENYLMERCAPTOACETIC ACID (4)

			Amines		Oxalates		Hydrochlorides	
No.	R	R′	Yield,[a] %	Bp (mm), °C	Mp, °C	Formula[c]	Mp, °C	Formula[c]
1	H	$OCH_2CH_2N(CH_3)_2$	87	143–144 (2.0)	110–111	$C_{14}H_{19}NO_6S$	104–105	$C_{12}H_{18}ClNO_2S$
2	H	$OCH_2CH_2N(C_2H_5)_2$	82	134–135 (0.15)	82–83	$C_{16}H_{23}NO_6S$	82–84	$C_{14}H_{22}ClNO_2S$
3	H	$OCH(CH_3)CH_2N(CH_3)_2$	80	130–131 (1.0)	125–126	$C_{15}H_{21}NO_6S$	89–90	$C_{13}H_{20}ClNO_2S$
4	H	$OCH_2CH_2NC_6H_5$	71	150–152 (0.2)	130–131	$C_{17}H_{23}NO_6S$	109–110	$C_{15}H_{22}ClNO_2S$
5	H	$OCH_2CH_2NC_6H_4O$-*p*	75	168–169 (0.3)	127–128	$C_{16}H_{21}NO_7S$	107–108	$C_{14}H_{20}ClNO_3S$
6	H	$NHCH_2CH_2N(CH_3)_2$	76[b]		133–134	$C_{14}H_{20}N_2O_5S$	106–107	$C_{12}H_{19}ClN_2OS$
7	H	$NHCH_2CH_2N(C_2H_5)_2$	80[b]		117–118	$C_{16}H_{24}N_2O_5S$	82–83	$C_{14}H_{23}ClN_2OS$
8	CH_3	$OCH_2CH_2N(CH_3)_2$	90	134–136 (0.3)	126–127	$C_{15}H_{21}NO_6S$	113–114	$C_{13}H_{20}ClNO_2S$
9	CH_3	$OCH_2CH_2N(C_2H_5)_2$	93	152–153 (0.3)	102–103	$C_{17}H_{23}NO_6S$	96–98	$C_{15}H_{24}ClNO_2S$
10	CH_3	$OCH(CH_3)CH_2N(CH_3)_2$	95	131–132 (0.4)	127–128	$C_{16}H_{23}NO_6S$	109–111	$C_{14}H_{22}ClNO_2S$
11	CH_3	$OCH_2CH_2NC_6H_5$	84	162–164 (0.3)	132–133	$C_{18}H_{25}NO_6S$	120–121	$C_{16}H_{24}ClNO_2S$
12	CH_3	$OCH_2CH_2NC_6H_4O$-*p*	85	177–179 (0.4)	120–121	$C_{17}H_{23}NO_7S$	92–93	$C_{15}H_{22}ClNO_3S$
13	Cl	$OCH(CH_3)CH_2N(CH_3)_2$	95	143–144 (0.6)	131–132	$C_{15}H_{20}ClNO_6S$	118–119	$C_{13}H_{19}Cl_2NO_2S$[d]
14	Cl	$OCH_2CH_2N(C_2H_5)_2$	84	155–156 (0.4)	105–106	$C_{16}H_{22}ClNO_6S$	96–97	$C_{14}H_{21}Cl_2NO_2S$[d]
15	Cl	$OCH_2CH_2NC_6H_5$	76	173–175 (0.3)	135–136	$C_{17}H_{22}ClNO_6S$	132–133	$C_{15}H_{21}Cl_2NO_2S$[d]
16	Cl	$OCH_2CH_2NC_6H_4O$-*p*	71	195–197 (0.6)	122–123	$C_{16}H_{20}ClNO_7S$	146–147	$C_{14}H_{19}Cl\ NO_3S$[d]
17	CH_3	$NHCH_2CH_2N(CH_3)_2$	86[b]		165–166	$C_{15}H_{22}N_2O_5S$	108–109	$C_{13}H_{21}ClN_2OS$

[a] Purified bases. [b] Unpurified bases. [c] Oxalates were analyzed for C, H, N and hydrochlorides for N, S, Cl. The anal results obtained for those elements were within ±0.4% of the theoret value. [d] Calcd for total Cl.

TABLE II
PRELIMINARY PHARMACOLOGIC ACTIVITY. PRIMARY MOUSE SCREEN[a]

No.	LD_{50}	MED_{50}	LD_{50}/MED_{50}	Major overt effect	Duration of effect, min
1	>100	5.6	>17.8	Motor deficit, ataxia, CNS depression	60
2	>100	10.0	>10	Motor deficit, ataxia, CNS depression	60
3	79.4	3.2	25.1	Motor deficit, ataxia, CNS depression	60
4	>100	10.0	>10	Motor deficit, ataxia, CNS depression	60
5	>100	17.8	>5.6	Motor deficit, ataxia, CNS depression, decreased muscle tone	30
6	>100	10	>10	CNS depression, decreased locomotion	60
7	>100	10	>10	CNS depression, decreased locomotion	60
8	>100	17.8	>5.6	CNS depression, ataxia	30
9	>100	5.6	>17.6	CNS depression, ataxia	30
10	89.1	1.8	50.1	CNS depression, ataxia	30
11	>100	10	>10	CNS depression, ataxia	60
12	>100	5.6	>17.8	CNS depression, motor deficit	60
13		17.8	>5.6	Decreased locomotion	60
14	>100	31.6	>3.2	Decreased muscle tone	60
15	>100	1.8	>5.6	Low carriage, ataxia	60
16	>100	5.6	>17.8	CNS depression, motor deficit	60
17	>100	17.8	>5.6	Decreased locomotion	60

[a] Dose levels are in mg/kg of body wt.

was employed to calc the minimal effective dose (MED_{50}). The ratio of the median lethal dose (LD_{50}) to the MED_{50} was detd for each compd. Preliminary pharmacologic evaluations are listed in Table II.

Neuropharmacological Profile of 1-Azaphenothiazine-10-thiolcarboxylates

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During a study of compounds having both a high pharmacological activity and a high therapeutic index we were attracted by published data[1,2] on certain 1-azaphenothiazine derivatives.[3] In particular 2-(diisopropylamino)ethyl 1-azaphenothiazine-10-thiolcarboxylate (**1**, Table I) was reported to have an anticholinergic activity 8 times that of atropine and a spasmolytic activity 9 times that of papaverine.[4] In addition to establishing a pharmacological profile of **1** we studied the compds **2–6**, which were derived from other aminothiols, and also 4 substitution products (**7–10**) of **1**. The substituent groups in **7–9** were

(1) W. A. Schuler and H. Klebe, *Justus Liebigs Ann. Chem.*, **653**, 172 (1962).

(2) W. A. Schuler, H. Klebe, and A. von Schlichtegroll, *ibid.*, **673**, 102 (1964).

(3) The nomenclature used throughout this paper is that described in the IUPAC 1957 Rules (*J. Amer. Chem. Soc.*, **82**, 5545 (1960); see Table I). Chemical Abstracts indexes this series as 10*H*-pyrido[2,3-*b*][1,4]benzothiazines.

(4) We wish to thank Dr. Roger Gaudry of Ayerst, McKenna and Harrison, Ltd., Montreal, Canada, for calling our attention to this class of compd and for providing us with a sample of the maleate salt for our preliminary evaluation.