Experimental Section[9]

2-(4-Pyridyl)-5-*n*-propylaminothiadiazole.—N^1-Isonicotinoyl-N^4-*n*-propylthiosemicarbazide (2.38 g, 0.01 mole) was added to concd H_2SO_4 (5 ml) in small portions. The mixt was shaken vigorously to form an homogeneous soln and set aside (30 min). It was then poured in ice water and neutralized (Na_2CO_3). The product was collected and crystd (EtOH), to form yellow shining needles. Other compds (Table I) were prepd similarly.

5-*p*-(1-Cyclohexylureidosulfonyl)phenyl-4-ethyl-4*H*-1,2,4-triazole-3-thiol.—4-Ethyl-5-*p*-sulfamoyl-phenyl-4*H*-1,2,4-triazole-3-thiol (2.15 g, 0.01 mole) was dissolved in dry Me_2CO (50 ml). To this soln were added anhyd K_2CO_3 (4.0 g) and cyclohexyl isocyanate (1.5 ml), and the mixt was refluxed on steam bath for 8 hr. Acetone was distd off, and the residue was dissolved in H_2O, filtd, cooled, and acidified (HCl), when a sticky material sepd which solidified after long standing. It was filtd, washed (H_2O), and crystd (EtOH). Other sulfonylureas were prepd by following the above procedure.

Acknowledgments.—We wish to thank Mr. M. T. Jaokar and coworkers for the microanalyses and Dr. N. K. Dutta, Director, Haffkine Institute, for his interest in this work.

(9) The melting points are capillary melting points and are uncor. Analyses indicated by symbols of the elements were within ±0.4% of the theor values.

Potential Acetylcholinesterase Reactivators. *p,p'*-Biphenyl and 1,4-Benzene Disubstituted Oximes[1a,b]

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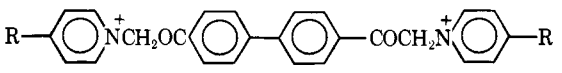
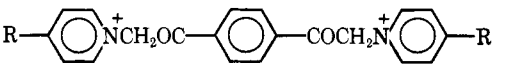
In 1954 Long and Schueler[2] reported the potent AChE inhibition caused by *p,p'*-bis(pyridiniumacetyl)-biphenyl dibromide (**1a**). Later, the relative AChE inhibition of a series of substituted pyridinium and *N*-methylpiperidinium compds was determined.[3] These studies suggested that *p,p'*-bis(substituted acetyl)-biphenyl possessed desirable features for binding with AChE.



·2Br⁻

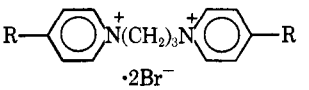
1a, R = H
1b, R = CH=NOH

As part of our continuing studies on AChE reactivators, *p,p'*-bis(pyridinium-4-aldoxime acetyl)biphenyl dibromide (**1b**) and *syn,syn*-1,4-bis(pyridinium-4-carbaldoxime acetyl)benzene (**2a**) were synthesized, the oxime configurations assigned, and the reactivator potency determined relative to TMB-4 (**3a**), 2- and 4-pyridinecarbaldoximes methylhalides (PAM's).



·2Br⁻

2a, R = CH=NOH
2b, R = H



·2Br⁻

3a, R = CH=NOH
3b, R = H

The configuration assignment are based upon the work of Poziomek and coworkers[4] who synthesized and characterized *syn*- and *anti*-4-pyridinecarbaldoxime and the corresponding methiodides. Kirtz, *et al.*,[5] reported that 4-PAM had 0.01 the potency of 2-PAM. In our labs,[1a] the *syn*-4-PAM was found to be 0.01 the potency of 2-PAM. Using combined nmr and biochemical assay techniques, it was possible to determine that **2a** and **3a** are syn,syn'. Since the starting oxime and the method of synthesis are the same for **1b**, it may be inferred that the configuration of **1b** is also syn,syn'.

1b, **2a**, and **3a** were evaluated for their ability to reactivate electric eel AChE inhibited with diethyphosphorylthiocholine according to the procedure previously described.[1a] Pralidoxime (2-pyridinecarbaldoxime methyl chloride, 2-PAM) was utilized as the standard. Since the effectiveness of an AChE reactivator is limited by its ability to inhibit AChE, the inhibitor potency of **1b**, **2a**, **3a**, and 2-PAM together with the inhibitor potency of the corresponding noroximino compds (**1a**, **2b**, and **3b**) was determined. The reactivation and inhibition data is summarized in Table I.

TABLE I
REACTIVATION AND INHIBITION OF ELECTRIC EEL ACHE

	Relative potency as reactivator	ID_{50}[b]
2-PAM	1.0	8.1×10^{-4}
1b	0.63 (0.62–0.64)[a]	9.9×10^{-7}
1a		6.6×10^{-9}
2a	0.55 (0.46–0.64)[a]	2.7×10^{-6}
2b		8.7×10^{-7}
3a	4.8 (4.2–5.4)[a]	6.4×10^{-4}
3b		1.9×10^{-3}

[a] 95% fiducial limits. [b] Molar concentration at which the enzyme is 50% inhibited.

TABLE II

No.	% yield	Mp, °C	Formula[a]	Synthesis method
1b	70	235–237	$C_{28}H_{24}N_4O_4Br_2$	A
2a	75	203–205 dec	$C_{22}H_{20}N_4O_4Br_2$	A
2b	80	220 dec	$C_{20}H_{18}N_2O_2Br_2$	A
3a		246[b]		*b*
3b	51	228–231[c]	$C_{13}H_{16}N_2Br_2$	A

[a] All compds analyzed corrected for C, H, N. [b] Lit. 238–241° [E. J. Poziomek, B. F. Hackley, and G. M. Steinberg, *J. Org. Chem.*, **23**, 714 (1958)]. [c] Lit. 220–221° [J. Hartwell and M. H. Pogorelsken, *J. Amer. Chem. Soc.*, **72**, 2040 (1950)].

(1) (a) Previous paper: C. F. Barfknecht, F. W. Benz, and J. P. Long, *J. Pharm. Sci.*, **60**, 138 (1971); (b) this work was supported in part by National Institutes of Health Research Grants NB-01396 and NB-4430.

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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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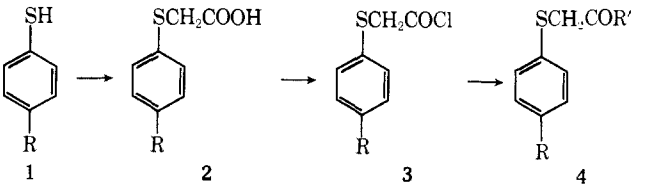
Esters and amides of phenoxyacetic acid and their derivatives[1-5] possess a wide spectrum of biol activity. The diethylaminoethylamide of *p*-chlorophenoxyacetic acid demonstrated antidepressant, analgetic, and local anesthetic properties that were comparable and in some instances greater than that 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]

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