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	$C_{17}H_{25}NO_6S$	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).

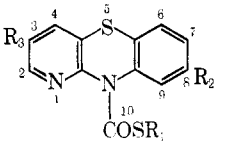
(2) W. A. Schuler, H. Klebe, and A. von Schlichtegroll, *ibid.*, **673**, 102 (1964).

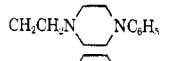
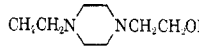
(3) The nomenclature used throughout this paper is that described in the IUPAC 1957 Rules (*J. Amer. Chem. Soc.*, **82**, 5545 (1960); see Table I). Chemical Abstracts indexes this series as 10*H*-pyrido[2,3-*b*][1,4]benzothiazines.

(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.

TABLE I

1-AZAPHENOTHIAZINE-10-THIOLCARBOXYLATES



Compd	R_1	R_2	R_3	Mp, °C	Recrystn solvent	Yield,[a] %	Formula	Analyses[b]
1	$CH_2CH_2N(i\text{-}C_3H_7)_2$	H	H	141–142	*i*-PrOH	85	$C_{20}H_{25}N_3OS \cdot Mal$[c]	C, H, N, S
2	$CH_2CH_2NHCOCH_3$	H	H	131–133	Toluene	43	$C_{16}H_{15}N_3O_2S_2$	C, H, N, S
3	$CH_2CH_2CONHNHCOCH_3$	H	H	220–221	Dioxane	47	$C_{16}H_{13}N_4O_3S_2$	C, H, N, S
4	$CH_2CH_2CON(NHCOCH_2CH_2)H$	H	H	257–258	*d*	95	$C_{28}H_{20}N_6O_4S_4$	C, H, N, S
5		H	H	183–184	Dioxane	26	$C_{24}H_{24}N_4OS_2$	C, H, N, S
6		H	H	245–246 dec	EtOH	18	$C_{20}H_{24}N_4O_2S_2 \cdot 2HCl$	C, H, Cl, N, S
7	$CH_2CH_2N(i\text{-}C_3H_7)_2$	F	H	152–153	EtOAc	29	$C_{20}H_{24}FN_3OS_2 \cdot Mal$[c,e]	C, H, N, S
8	$CH_2CH_2N(i\text{-}C_3H_7)_2$	SCH_3	H	106–108	Me_2CO–H_2O	42	$C_{21}H_{27}N_3OS_3$	C, H, N, S
9	$CH_2CH_2N(i\text{-}C_3H_7)_2$	CF_3	H	80–82	Me_2CO–H_2O	42	$C_{21}H_{24}F_3N_3S_2O$	C, H, F, N, S
10[f]	$CH_2CH_2N(i\text{-}C_3H_7)_2$	H	Cl	193			$C_{20}H_{24}ClN_3OS_2 \cdot HCl$	

[a] Yields reported are those of recrystd product. No attempt was made to improve reaction or work-up condns. [b] Values for the elements indicated were within 0.4% of theoretical. [c] Mal = maleic acid, $C_4H_4O_4$. Maleate salts were pptd from Et_2O solutions of the base. [d] Insol in all common solvents; leached with boiling EtOAc. [e] The free base was a colorless solid, mp 64–65° (hexane). [f] Obtd through the courtesy of W. A. Schuler, Chemiewerk Hamburg (Degussa).[7,14]

chosen because of their involvement in structure–activity relationships in the phenothiazine series[5] and in the 1-azaphenothiazine series.[6–8] Compd **10**, which was commercially available, was chosen as an example of a compd having the same ester group as **1** and **7–9** but having a substituent in the 3, rather than the 8, position.

Chemistry.—Compds **1–6** were made by the reaction of 1-azaphenothiazine-10-carbonyl chloride[2] with the appropriate thiols. The 8-substituted 1-azaphenothiazine precursors of **7–9** were prepared by thionation of the appropriately substituted anilinopyridines. We believe that thionation proceeded to give the substituent in the 8 position rather than in the alternative 6 position even though analogous cyclizations in the phenothiazine series are sometimes known to give two isomeric products.[9–11] Literature data show that a variety of 8-substituted 1-azaphenothiazines have melting points quite similar to those of phenothiazines bearing the same substituents in the analogous 3 position; these similarities were observed with our 1-azaphenothiazines. The structures assigned are also supported by ir data. Our novel substituted 1-azaphenothiazines all showed absorption at 800–850 cm^{-1}, which is characteristic of 8-substituted 1-azaphenothiazines and 3-substituted phenothiazines, but which is not characteristic of the isomeric compds with substituents in the 6 position.[6,10–12]

Attempts to prepare 8-chloro- and 8-methoxy-1-azaphenothiazines were abandoned when we were unable to isolate recognizable products from the thionation of the respective anilinopyridines.

Pharmacology.—Compds were evaluated for neuropharmacological activity in a modified Irwin mouse profile[13] (Table II). It was apparent that the thiol esters derived from compds other than 2-(diisopropylamino)ethanethiol (**2–6**) were considerably less active than **1**, while **7–10**, derived from the same thiol as **1**, retained significant activity in this test. No significant effect on reactive signs or potency was observed in **10** where the substituent was in the 3 position; the modest nonspecific activity of **10** was in contrast to the high activity we observed with another 3-chloro-1-azaphenothiazine having an entirely different substituent at the 10 position (3-chloro-10[3-[4-(2-hydroxyphenyl)piperazin-1-yl]propyl]-1-azaphenothiazine dihydrochloride (cloxypendyl);[14] MED_{50} 0.24 mg/kg (0.13–0.42), LD_{50} 63 mg/kg (50–70)).

Compd **1** had a hypotensive MED_{50} of 0.3 mg/kg in the anesthetized cat; the effect was not dose related and no effect on respiration or heart rates was observed in the dose range studied. When administered at 100 μg/kg iv to rats simultaneously with 200 μg/kg of epinephrine (approximately 3 times the LD_{50}) **1** was inactive as an adrenolytic; in this same test chlorpromazine had an ED_{50} of 21 μg/kg.[15]

Compds **1** and **3–7** all failed to potentiate hexobar-

(5) E. F. Domino, R. D. Hudson, and G. Zografi in "Drugs Affecting the Central Nervous System" A. Burger, Ed., M. Dekker, New York, N. Y., 1968, p 327, and ref cited therein.

(6) J.-P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Reusch, S. Guldimann, V. Theus, and E. Schenker, *Helv. Chim. Acta*, **42**, 2541 (1959).

(7) Degussa Belgian Patent 630,970 (1963); *Chem. Abstr.*, **61**, 4382g (1964).

(8) Z. Ledochowski, M. Bogucka, and B. Wysocka-Skrzela, *Rocz. Chem.*, **38**, 311 (1964); *Chem. Abstr.*, **61**, 4341 (1964).

(9) H. L. Yale, F. Sowinski, and J. Bernstein, *J. Amer. Chem. Soc.*, **79**, 4375 (1957).

(10) A. Roe and W. F. Little, *J. Org. Chem.*, **20**, 1577 (1955).

(11) J.-P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Reusch, S. Guldimann, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta*, **41**, 1061 (1958).

(12) D. Chandra, V. N. Sharma, and R. L. Mital, *Can. J. Chem.*, **45**, 761 (1967).

(13) S. Irwin, *Psychopharmacologia*, **13**, 222 (1968).

(14) A. Gross, K. Thiele, W. A. Schuler, and A. von Schlichtegroll, *Arzneim.-Forsch.*, **18**, 435 (1968).

(15) F. P. Luduena, E. O'Malley, and I. H. Oyen, *Arch. Int. Pharmacodyn. Ther.*, **122**, 111 (1959).

TABLE II

MOUSE PROFILE DATA[a]

Compd	MED50,[b] mg/kg (iv) (fiducial limits)	LD50, mg/kg (iv) (fiducial limits)	Reactive signs at MED50
1	0.056 (0.034–0.094)	11.2[c] (8.9–14.0)	Mydriasis; motor deficits
2	5.6 (1.8–18.0)	>32	Motor deficits
3	>32		
4	>10		
5	5.6 (1.8–18.0)	>10	Decreased activity; decreased sensitivity to touch; ataxia
6	5.6 (1.8–18.0)	56 (18–180)	Mydriasis
7	0.18 (0.11–0.30)	13 (10–16)	Mydriasis; motor deficits
8	1.8 (0.56–5.6)	10 (3.2–32.0)	Mydriasis; increased respiration rate; motor deficits
9	1.8 (0.56–5.6)	18 (5.6–56.0)	Increased sensitivity to touch; others as compound 8
10	1.8 (056–5.6)	18 (5.6–56.0)	Mydriasis; increased locomotor activity; motor deficits

[a] Charles River Swiss male mice were used (2–4 animals/dose) in a procedure similar to that described in ref 13. Compounds were administered iv in the following solvents: H_2O (**6**, **10**); 0.1 *N* HCl (**1**, **8**, **9**); 15% v/v DMSO–H_2O (**5**, **3**, **7**); 25% v/v polyethyleneglycol 300 (**2**); 25% v/v polyethylene glycol 200 (**4**). [b] Minimum dose at which reactive signs were observed in half of mice tested. [c] Ref 2 reported 117 mg/kg, ip.

bital[16] and to block pentylenetetrazole or electroshock[17] at 10 mg/kg iv or po; **1** and **7** were additionally inactive even at 100 mg/kg po.

In overt behavior tests[18] **1** caused severe depression in mice, dogs, and monkeys at 0.01–0.056 mg/kg iv. In cats **1** caused vocalization and ataxia at 25 μg/kg, while **2** caused only a slight depression at 1 mg/kg. In monkeys **1** caused a slight depression at 10 μg/kg and **2** a transient excitability at 1 mg/kg. Compd **7** was inactive in both the cat (100 μg/kg) and the monkey (1 mg/kg).

It was apparent that in this series **1** was by far the most active compd; its relative inactivity as an adrenolytic is in contrast to that of drugs in the phenothiazine series.

Experimental Section

Melting points were obtained in capillaries and are uncorrected. Elemental analyses were performed by Dr. S. M. Nagy (Belmont, Mass.). Satisfactory ir spectra were recorded for all compds in Table I.

Thiols.—The thiol intermediates for **1**–**4** and **7**–**9** were prepd by literature procedures.[19–21]

4-Phenylpiperazine-1-ethanethiol was prepd from *N*-phenylpiperazine by a procedure similar to that used for the prepn of 2-(diisopropylamino)ethanethiol.[19] The crude product was sepd from excess reagent by distg off the latter at 88–117° (0.3 mm). The undistd residue was dissolved in C_6H_6, the soln was filtered, and the oily product obtained in almost quant yield by evapn of the solvent. *Anal.* ($C_{12}H_{18}N_2S$) SH.

4-(2-Mercaptoethyl)piperazine-1-ethanol was prepd similarly from *N*-(2-hydroxyethyl)piperazine. The crude product was purified by distn at 137–140° (2 mm) and was obtained (77%) as colorless needles, mp 38–42°. *Anal.* ($C_8H_{18}N_2OS$) C, H, N, S, SH.

2-(3-Fluoroanilino)pyridine.—A mixt of 98 g (0.88 mole) of 3-fluoroaniline and 70 g (0.44 mole) of 2-bromopyridine was refluxed for 1.5 hr. The cooled mixt was made basic by addn of 10% NaOH and extd with Et_2O. From the dried ext there was obtained by dist a viscous oil, bp 135° (1.2 mm), that soon solidified to give 63.8 g (73%), mp 55–57° (EtOH–H_2O). *Anal.* ($C_{11}H_9FN$) C, H, F, N.

2-(3-Methylthioanilino)pyridine was prepd (65%) from 2-chloropyridine in a lit. procedure.[6]

2-(α,α,α-Trifluoro-*m*-toluidino)pyridine was prepd by a procedure similar to that used for the 3-F analog above. The crude product was washed free from excess *m*-aminobenzotrifluoride with hexane and then was recryst from EtOH to give 77% of colorless plates, mp 83–85°. *Anal.* ($C_{12}H_9F_3N_2$) C, H, F, N.

1-Azaphenothiazines were prepd by thionation of about 0.25 mole of the appropriate anilinopyridine.[1] In the unsubstituted case the yield was 40% but in the 3 remaining cases (8-fluoro-, mp 169–170° (*i*-PrOH), *Anal.* ($C_{11}H_7FN_2S$) C, H, N, S; 8-methylthio-, mp 138–140° (*i*-PrOH), lit.[6] 142–143°; 8-trifluoromethyl-, mp 188–190° (EtOH), *Anal.* ($C_{13}H_7F_3N_2S$) C, H, F, N, S) the yields were 10–20%. The mole ratio of S to amine was about 1.25. The use of equimolar quantities, as reported for an earlier prepn of the methylthio compd,[6] gave inferior yields.

1-Azaphenothiazine-10-carbonyl chlorides were prepd from 4–15 g of the appropriate 1-azaphenothiazines by a procedure described for the unsubstituted case:[2] 8-fluoro- (67%), mp 152–154° (toluene), *Anal.* ($C_{12}H_6ClFN_2OS$) C, H, Cl, F, N, S; 8-methylthio- (80%), mp 114–115° (C_6H_6–pentane), *Anal.* ($C_{13}H_9ClN_2OS_2$) C, H, Cl, N, S; 8-trifluoromethyl- (45%), mp 128–130° (C_6H_6–pentane), *Anal.* ($C_{13}H_6ClF_3N_2OS$) C, H, Cl, F, N, S.

Thiol Esters (Table I).—Compds **1**, **5**, **8**, and **9** were prepd by the reaction of 2–3 g of the appropriate carbonyl chloride with 1–4 equivs of the thiol in about 30 ml of refluxing C_6H_5Cl.[2] Compds **2**, **3**, **4**, and **6** were prepd in about 75 ml of refluxing CH_2ClCH_2Cl. Compd **7** was prepd in about 30 ml of refluxing C_6H_6. All work-ups were conventional. Maleate salts were prepd in 2 cases when both the free base and the hydrochloride were too insol in solvents used in pharmacol testing.

Acknowledgment.—We wish to thank Dr. D. G. Teiger and Dr. S. P. Battista for technical assistance in pharmacology and David Levinson for assistance in chemical synthesis.

(16) C. A. Winter, *J. Pharmacol. Exp. Ther.*, **94**, 7 (1948); we used a subhypnotic dose of hexobarbital (40 mg/kg) rather than the fully hypnotic dose used by Winter.

(17) F. J. Rosenberg and J. A. Bottiroli, *Proc. Soc. Exp. Biol. Med.*, **115**, 410 (1964).

(18) L. O. Randall, W. Schallek, G. A. Heise, E. F. Keith, and R. E. Bagdon, *J. Pharmacol. Exp. Ther.*, **129**, 163 (1960); procedures similar to those described were used in our work.

(19) D. D. Reynolds, M. K. Massad, D. L. Fields, and D. L. Johnson, *J. Org. Chem.*, **26**, 5125 (1961).

(20) E. R. Atkinson, G. R. Handrick, R. J. Bruni, and F. E. Granchelli, *J. Med. Chem.*, **8**, 29 (1965).

(21) R. B. Martin, S. Lowey, E. L. Elson, and J. T. Edsall, *J. Amer. Chem. Soc.*, **81**, 5089 (1959).