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2-(Arylthio)ethanamines & α-(Arylthio)propionamides with Antidepressant Activity†

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Reaction of aziridine with thiophenols affords 2-arylthioethanamines; with 2-methylaziridine, ring opening occurs regiospecifically to provide 1-arylthio-2-propanamines. The structure of one member of this group, 1-(4-chlorophenylthio)-2-propanamine, (**7**) has been proved by other unambiguous syntheses. **7** and isomer **12** arise from the alkylation of 4-chlorothiophenol with 2-chloropropylamine as well as from the displacement of the tosyl group in 1-(4-chlorophenylthio)-2-tosyloxypropane (**13**). Alkylation of 4-chlorothiophenol with α-chloropropionamide affords **11** which leads to **12** on LAH reduction Ethanamines and propanamines are converted into guanidines, amides ureas and thioureas. Many arylthioethanamines, e.g. **7**, **22**, **28**, **38** and **39** (as HCL salts) and α-arylthiopropionamides, e.g. **11**, **86**, **91**, **93** and **96** exhibit good activity in the DOPA potentiation and reserpine antagonism tests. Among these, **7** HCl [1-(4-chlorophenylthio)-2-propanamine hydrochloride, C 2998-Go] is the most potent and does not inhibit rat brain MAO activity. In clinical trials, C 2998-Go compares favourably with imipramine.

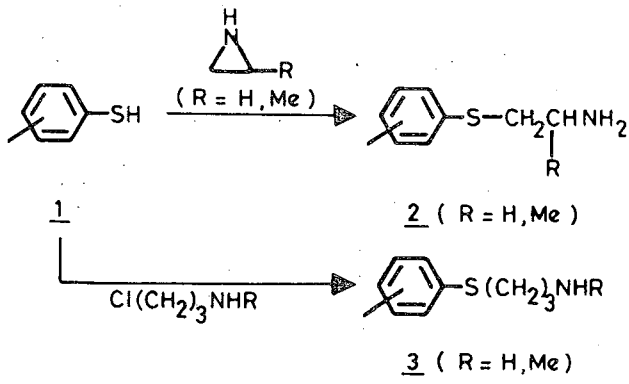
Among the nontricyclic antidepressants, aryl alkyl amines, aryloxy and arylthio alkyl amines and indolylalkyl amines have attracted considerable attention, but their MAO inhibitory activity has limited their clinical usefulness[1]. Representatives of the second group of compounds mentioned above consist of N-(2-chloro)- and N-(2,4-dichloro)phenoxyethyl-cyclopropyl amines and their thio analogues[2]. Some years ago we had come across a series of 2-(arylthio)ethanamines and 1-(arylthio)-2-propanamines wherein dissociation of antidepressant and MAO inhibitory activity appeared possible. C 2998-Go (**7**.HCl) arising from this work was taken up for clinical trials[3]. This paper describes synthesis and structure-activity relationship in this series.

Chemistry

2-(Arylthio)ethanamines and 1-(arylthio)-2-propanamines (**2**), including **7** were prepared by opening of aziridine ring by thiophenols (method-a), and are reported in Table 1. 3-(Arylthio)propanamines (**3**) were prepared from thiophenols and aminopropyl halides (method-b) (Table 2).

The former reaction seemed to occur regiospecifically presumably by attack of the aziridine by thiophenol at the less-hindered carbon atom. The structure of **7** was unambiguously established by the following syntheses.

The isomer **12** (Table 3) was prepared by LAH reduction of the amide (**11**). Ammonolysis of tosylate



(**13**) afforded **12** as the major and **7** as the minor products. Presumably episulphide (**14**) is formed as an intermediate and the cleavage occurs with ammonia regioselectively by attack at the less substituted carbon atom.

On the other hand, an attempt to alkylate **4** with 2-chloropropyl amine (method-b) resulted in an approximately 1 : 1 mixture of **7** and **12**, the latter by direct alkylation and the former through the intermediacy of propylenimine formed from the alkylating agent and ammonia.

1-(4-Chlorophenoxy)-2-propanamine (**15**) was made from 4-chlorophenoxyacetone via the oxime, while 1-(heterylthio)-2-propanamines (**16** and **18**) were made by method-a (Table 3).

Amines were converted into guanidines, amides, ureas and thioureas by standard techniques (Table 4). Some ureas were oxidised by H_2O_2 or $KMnO_4$ to sulphoxides and sulphones which were also obtained from the amines by oxidation followed by derivatisation.

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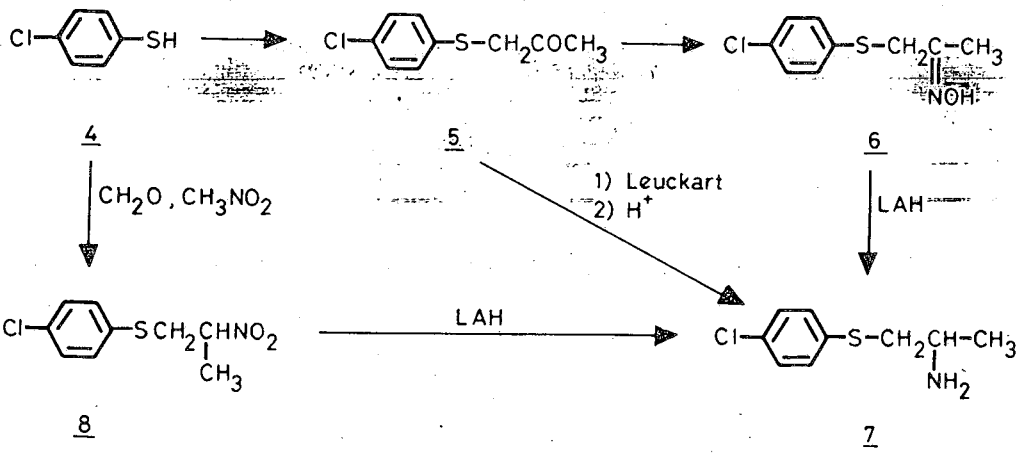
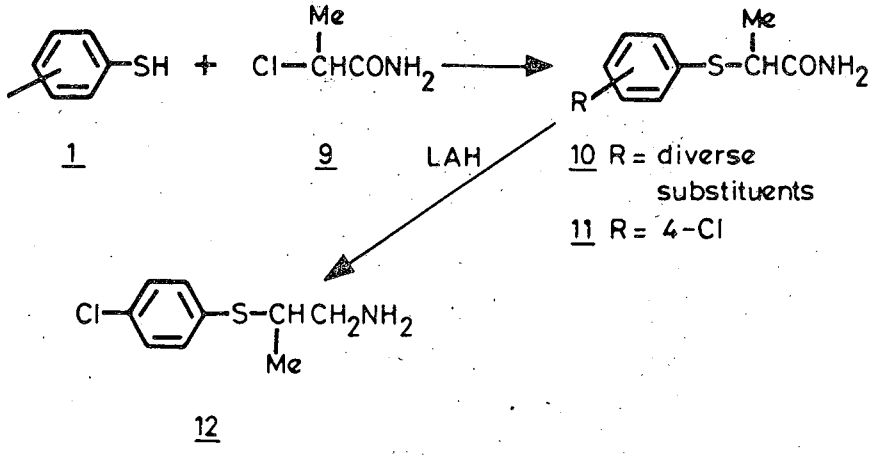
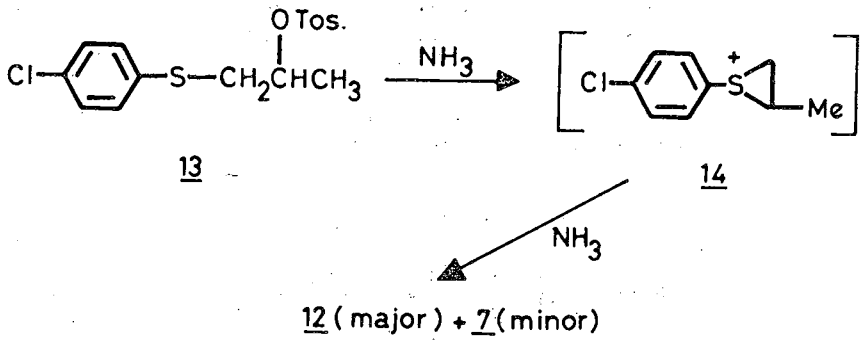
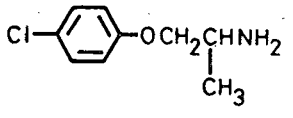








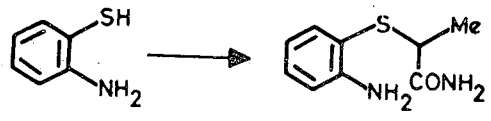
15

Het—S—CH_2CH_2NHR

16 Het = 2-benzoxazolyl
R = H

17 Het = 2-benzoxazolyl
R = CSNHPh

18 Het = 2-benzthiazolyl
R = H



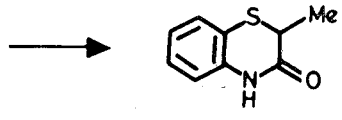
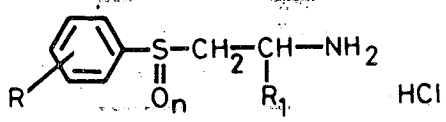


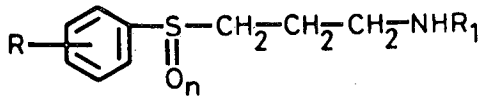
Table 1—2-Arylmercaptoethyl Amines, Sulphoxides and Sulphones



Compd	n	R	Mol. formula	Crystallised from	m.p. °C	Rating in dopa test[f] (ED_{50} mg/kg p.o.)	% Antagonism of reserpine-induced hypothermia[f] (ED_{50} mg/kg p.o.)
				$R_1 = H$			
22[a]	0	2-NH_2	$C_8H_{14}Cl_2N_2S$	EtOH-Et_2O	232-33	+ + +	47
23	0	2-CO_2H	$C_9H_{12}ClNSO_2$	EtOH-H_2O	247-48	+ +	29
24	0	2-CO_2Me	$C_{10}H_{14}ClNSO_2$	EtOH-Et_2O	158-59	Nil	24
25[b]	0	3-Me	$C_{13}H_{17}NSO_4$	EtOH-Et_2O	165-67	+	53
26[b]	0	4-Bu(t)	$C_{16}H_{23}NSO_4$	EtOH-Et_2O	149-51	Nil	9
27	0	4-Cl	$C_8H_{11}Cl_2NS$	EtOH-Et_2O	170-72	+ +	30
28[c]	0	4-Cl	$C_{10}H_{15}Cl_2NS$	EtOH	134-35	+ + + + +(12)	68(15)
29	0	4-Me	$C_9H_{14}ClNS$	MeOH-Et_2O	162-64	+ + +	50
30	1	2-CO_2Me	$C_{10}H_{14}ClNSO_3$	EtOH-Et_2O	180-81	Nil	39
31	1	4-Cl	$C_8H_{11}Cl_2NOS$	EtOH	194-95	Nil	Nil
32[d]	1	4-Cl	$C_{10}H_{15}Cl_2NOS.H_2O$	EtOH-Et_2O	203-5	—	—
33[e]	2	4-Cl	$C_8H_{11}Cl_2NO_2S$	EtOH-Et_2O	275-77	Nil	6
				$R_1 = CH_3$			
34	0	H	$C_9H_{14}ClNS$	EtOH-Et_2O	159	+	66
35	0	2-NH_2	$C_9H_{16}Cl_2N_2S$	EtOH	186-88	+	41
36	0	2-CO_2H	$C_{10}H_{14}ClNO_2S$	EtOH-Et_2O	216-18°	Nil	50
37	0	2-CO_2Me	$C_{11}H_{16}ClNO_2S$	EtOH-Et_2O	139-40		
38	0	2-Me	$C_{10}H_{16}ClNS$	EtOH-Et_2O	168-69	+ + + +(8)	66(13.5)
39	0	3-Cl	$C_9H_{13}Cl_2NS$	EtOH-Et_2O	122-24	+ + + +(10)	47(28.7)
40	0	3-Me	$C_{10}H_{16}ClNS$	C_6H_6	123-24	+	42
41	0	4-Br	$C_9H_{13}BrClNS$	EtOH-Et_2O	117-20	+ + +	—
42	0	4-Bu(t)	$C_{13}H_{22}ClNS$	EtOH-Et_2O	158-60	+ +	58
43	0	4-F	$C_9H_{13}ClFNS$	EtOH-Et_2O	132-33	+ +	40
44	0	4-Me	$C_{10}H_{16}ClNS$	C_6H_6-hexane	114-15	+	66
7	0	4-Cl	$C_9H_{13}Cl_2NS$	EtOH-Et_2O	149-51	+ + + +(8.6)	86(2.5)

(a) di-HCl not tested; (b) maleate; (c), (d) N,N-dimethyl- **27** and **31** respectively; and (e) phthalimide, m.p. 160-61° (Found: C, 55.2; H, 3.5. $C_{16}H_{12}NO_4S$ requires C, 54.9; H, 3.5%); (f)-, not tested; nil, inactive at dose tested.

Table 2—Arylmercaptopropylamines and Derivatives



Compd	n	R	R_1	Mol. formula	Crystallised from	m.p. °C	Rating in dopa test (ED_{50} mg/kg p.o.)	% Antagonism of reserpine-induced hypothermia (ED_{50} mg/kg p.o.)
99[+]	0	H	H	$C_9H_{14}ClNS$	EtOH-Et_2O	181-82	Nil**	—
100*	0	2-CO_2Me	H	$C_{15}H_{19}NO_6S$	EtOH-Et_2O	121-22	Nil	—
101[+]	0	4-Cl	H	$C_9H_{13}Cl_2NS$	EtOH-Et_2O	219-20	Nil**	—
102[+]	0	4-Cl	Me	$C_{10}H_{15}Cl_2NS$	EtOH-Et_2O	134-35		
103	0	4-Cl	COCH=CHPh	$C_{18}H_{18}ClNOS$	EtOH	135-36	+	21
104	2	4-Cl	H	$C_9H_{13}Cl_2NO_2S$	EtOH	196-98	Nil	9

[+]HCl.
*maleate
**toxic convulsions.

Table 3—Miscellaneous Thio and Oxypropanamines and Thiazinones

Compd	Mol. formula	Crystallised from	m.p. °C	Rating in dopa test (ED_{50} mg/kg p.o.)	% Antagonism of reserpine-induced hypothermia (ED_{50} mg/kg p.o.)
12.HCl	$C_9H_{13}ClNS$	EtOH	176-77	+	23
15.HCl	$C_9H_{13}Cl_2NO$	EtOH-Et_2O	183-84	+ + +	—
16.HCl.$\frac{1}{2}H_2O$	$C_9H_{11}ClN_2OS$	EtOH-Et_2O	151-52	—	—
16	$C_9H_{10}N_2SO$	EtOH	199-200	—	—
17	$C_{16}H_{15}N_3OS_2$	EtOH	135-38	+	55
18.H_2O	$C_{10}H_{13}ClN_2S_2$	EtOH-Et_2O	163-65	—	—
21	C_9H_9NOS	Et$_2$O exchange	130-31	—	—

α-Arylthiopropionamides, listed in Table 5 were prepared from thiophenols and α-chloropropionamide. In this reaction 2-aminothiophenol (**19**) was converted into the thiazinone (**21**) obviously through the intermediate amide (**20**).

3-(Arylthio)propanamines made by method-b and some derivatives are listed in Table 2.

Pharmacology

Compounds were administered orally (p.o.) in 0.2 % agar suspension to CF male mice. They were tested at a dose of 25 mg/kg p.o. for their activity in the mouse DOPA response potentiation test[4] and for their ability to antagonise reserpine-induced hypothermia[5]. For highly active compounds, ED_{50} values were determined. Results are entered in Tables 1-5.

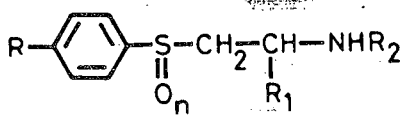
Structure-activity relationship

Compounds belonging to 2-(arylthio)ethanamine and 1-(arylthio)-2-propanamine series (Table 1) generally exhibited interesting activity in the two tests. Among the former group, **22** carrying an *ortho*-amino group in the phenyl ring and **29**, the 4-methyl analogue were moderately active. The 4-chloroderivative **27** was only weakly active, but the N,N-dimethyl compound **28** was very potent. In the 1-(arylthio)-2-propanamine series, good activity in both tests was seen for the 2-methyl (**38**), 3-chloro (**39**) and 4-chloro (**7**) derivatives. However, **7** (C 2998-Go) scored over all other highly active compounds in terms of ED_{50} values. In the DOPA test, it was significantly superior to **28** and **39**, but marginally inferior to **38**, however, in the reserpine antagonism test, it surpassed all these in the ED_{50} value. Many functional derivatives of these amines, such as guanidines, amides, ureas and thioureas were devoid of any significant activity (Table 4). Noteworthy in this respect are aryl ureas **78**, **79** and **81** of **7**, although the cinnamamide (**80**) retained some potency. The linear isomer **101** of **7** was totally devoid of activity in the two tests. Patent literature claims bactericidal and fungicidal properties for **101**[6]. Substitution of sulphur in **7** by oxygen (as in **15**) resulted in fall in activity.

Interestingly **12**, the position isomer of **7** was considerably weaker than **7**, whereas the precursor, α-(4-chlorophenylthio)propionamide (**11**) was potent in both tests (Table 5). In fact in this group of compounds, desired activities were fairly widely prevalent in both tests. Thus in addition to the 4-chloro derivative (**11**), the 3-methyl (**86**), pentachlorophenyl (**91**), benzyl (**93**) and 2-benzoxazolyl (**96**) analogues were quite potent. All were however inferior to **7** in terms of ED_{50} values in the two tests. Compound **11** was about equal to **7** in efficacy in the DOPA test (ED_{50}, 11 mg) but was only about one-sixth as potent in the reserpine antagonism test (ED_{50} 14 mg).

The best compound of the series, **7**.HCl (C 2998-Go) was weaker than tranylcypromine (ED_{50}-DOPA test, 1 mg; reserpine antagonism test, 0.8 mg), but was easily differentiated in that it had no debilitating *in vivo* MAO inhibitory activity[7]. Thus **7**.HCl did not inhibit rat brain MAO to any significant extent at 50 mg/kg i.p. 3 hours after pretreatment. Hence it was taken up for further development and its pharmacological properties characterised well[8]. In acute toxicity studies the preparation was found to have LD_{50} value of about 600 mg/kg p.o. in mice and rats and between 100 and 200 mg/kg p.o. in dogs. In a thirty-day study no mortality was observed in rats upto 200 mg/kg/day p.o. and in dogs upto 75 mg/kg/day p.o.[9]. Pharmacokinetics and metabolism studies were carried out with material labelled on the methylene carbon atom[10]. C

Table 4—Acyl, Carbamoyl, Thiocarbamoyl and Guanidine Derivatives of Arylmercaptoethyl Amines



Compd	*n*	R	R_2	Mol. formula	Crystallised from	m.p. (°C)	Rating in dopa test (ED_{50} mg/kg p.o.)	% Antagonism of reserpine-induced hypothermia (ED_{50} mg/kg p.o.)
				R_1 = H				
45. $\frac{1}{2}H_2SO_4$	0	H	$NH=C(-NH_2)$	$C_9H_{13}NOS.\frac{1}{2}H_2SO_4$	EtOH-Et_2O	170	++	Nil
46	0	H	COCH=CHPh	$C_{17}H_{17}NSO$	EtOH-H_2O	102-4	Nil	35
47	0	H	CONHPh	$C_{15}H_{16}N_2OS$	EtOH	121-22	Nil	—
48	0	H	CSNHPh	$C_{15}H_{16}N_2S_2$	EtOH-H_2O	116-17	++	27
49	0	2-NH_2	CONHPh	$C_{15}H_{17}N_3OS$	C_6H_6-hexane	199-200	—	—
50	0	3-Me	CSNHPh	$C_{16}H_{18}N_2S_2$	C_6H_6-hexane	110-12	Nil	39
51 $\frac{1}{2}H_2SO_4$	0	4-Cl	$HN=C(-NH_2)$	$C_9H_{12}ClN_3S.\frac{1}{2}H_2SO_4$	H_2O	190-91	Nil	28
52	0	4-Cl	COPh	$C_{15}H_{14}ClNOS$	C_6H_6-	85-86	Nil	8
53	0	4-Cl	CONH=CHPh	$C_{17}H_{16}ClNOS$	EtOH-H_2O	94-95	++	6
54. 2HCl	0	4-Cl	4-Me-piperazino-acetyl .2HCl	$C_{15}H_{24}Cl_3N_2OS$	EtOH-Et_2O	200-205	Nil	Nil
55. 2HCl. $2H_2O$	0	4-Cl	2-(4-Me-piperazino-ethyl.2HCl	$C_{15}H_{26}Cl_3N_3S$	EtOH	198-202	Nil	20
56	0	4-Cl	CSNHCH$_2$CH=CH_2	$C_{12}H_{15}ClN_2S_2$	Hexane	61-62	—	—
57	0	4-Cl	CONHPh	$C_{15}H_{15}ClN_2OS$	EtOH-H_2O	111-12	—	—
58	1	4-Cl	CSNHPh	$C_{15}H_{15}ClN_2OS_2$	EtOH	150-53	++	72
59	2	4-Cl	CONHPh	$C_{15}H_{15}ClN_2O_3S$	EtOH	183-85	Nil	Nil
60	2	4-Cl	$CONHC_6H_4CH_3(4)$	$C_{16}H_{17}ClN_2O_3S$	EtOH-DMF	196-97	—	—
61	2	4-Cl	$CONHC_6H_4Cl(4)$	$C_{15}H_{14}Cl_2N_2O_3S$	EtOH-DMF	206-7	—	—
62	2	4-Cl	CSNHPh	$C_{15}H_{15}ClN_2O_2S_2$	EtOH-DMF	177-78	—	—
63	2	4-Cl	$CONHC_6H_5CH_3(2)$	$C_{16}H_{17}ClN_2O_3S$	EtOH-DMF	202-3	—	—
64	2	4-Cl	CSNHBu(n)	$C_{13}H_{19}ClN_2O_2S_2$	EtOH-H_2O	92-93	—	—
65	2	4-Cl	$HN=C(-NH_2)$	$C_9H_{12}ClN_3O_2S.\frac{1}{2}H_2SO_4$	H_2O-EtOH	261-65	—	22
				R_1 = Me				
66	0	H	CONHPh	$C_{16}H_{18}N_2OS$	C_6H_6-hexane	109-10	—	—
67	2	H	CONHPh	$C_{16}H_{18}N_2O_3S$	EtOH-H_2O	113-15	—	—
68	0	2-NHCSNH$C_6H_4Cl(4)$	$CSNHC_6H_4Cl(4)$	$C_{23}H_{22}Cl_2N_4S_3$	EtOH	160-62	—	—
69	0	3-Me	$CONHC_6H_4CH_3(2)$	$C_{18}H_{22}N_2OS$	C_6H_6-hexane	117-18	—	—
70	0	3-Me	CONHPh	$C_{17}H_{20}N_2OS$	C_6H_6-hexane	106-7	—	—
71	0	3-Me	$CONHC_6H_4Cl(4)$	$C_{17}H_{19}ClN_2OS$	C_6H_6-hexane	120-22	—	—
72	0	3-Me	$CONHC_6H_4Me(4)$	$C_{18}H_{22}N_2OS$	C_6H_6-hexane	93-95	—	—
73	2	3-Me	CONHPh	$C_{17}H_{20}N_2O_3S$	EtOH-H_2O	142-43	—	—
74	2	3-Me	$CONHC_6H_4Me(2)$	$C_{18}H_{22}N_2O_3S$	C_6H_6	127-28	—	—
75	2	3-Me	$CONHC_6H_4Cl(4)$	$C_{17}H_{19}ClN_2O_3S$	EtOH	155-58	—	—
76	0	4-Bu(t)	$CONHC_6H_4Me(4)$	$C_{21}H_{28}N_2OS$	EtOH-H_2O	98-99	—	—
77	0	4-Bu(t)	$CONHC_6H_4Me(2)$	$C_{21}H_{28}N_2OS$	C_6H_6-hexane	148-49	—	—
78	0	4-Cl	CONHPh	$C_{16}H_{17}ClN_2OS$	EtOH-H_2O	102-3	+	35
79	0	4-Cl	$CONHC_6H_4Cl(4)$	$C_{16}H_{16}Cl_2N_2OS$	EtOH-H_2O	140-41	Nil	39
80	0	4-Cl	COCH=CHPh	$C_{18}H_{18}ClNOS$	C_6H_6-hexane	126-27	+++	55
81	1	4-Cl	CONHPh	$C_{16}H_{17}ClN_2O_2S$	C_6H_6-hexane	168-70	Nil	49
82	0	4-Me	CONHPh	$C_{17}H_{20}N_2OS$	EtOH-H_2O	99-101	++	45
83	0	4-Me	CSNHPh	$C_{17}H_{20}N_2S_2$	EtOH-H_2O	91-92		

Table 5—α-Mercaptoacetamides

$$R-S-\underset{\displaystyle R_1}{\underset{|}{CH}}-CO-NH_2$$

Compd	R	R^1	Mol. formula	Crystallised from	m.p. (°C)	Rating in dopa test (ED_{50} mg/kg p.o.)	% Antagonism of reserpine-induced hypothermia (ED_{50} mg/kg p.o.)
84	2-Me.C_6H_4-	Me	$C_{10}H_{13}NOS$	EtOH-H_2O	103-5	+ + +	—
85	2-CO_2Et.C_6H_4-	Me	$C_{12}H_{15}NO_3S$	THF-Et_2O	170-72	—	—
86	3-Me..C_6H_4-	Me	$C_{10}H_{13}NOS$	EtOH	112-14	+ + + +(15)	77(18)
87	4-Br.C_6H_4-	Me	$C_9H_{10}BrNOS$	EtOH	130-31	+ + +	32
11	4-Cl.C_6H_4-	Me	$C_9H_{10}ClNOS$	EtOH-H_2O	125-27	+ + + +(11)	75(14)
88	4-F.C_6H_4-	Me	$C_9H_{10}FNOS$	EtOH-H_2O	121-22	+ +	—
89	4-Me.C_6H_4-	Me	$C_{10}H_{13}NOS$	EtOH-H_2O	111-13	+ +	—
90	4-Bu(t).C_6H_4-	Me	$C_{13}H_{19}NOS$	EtOH-H_2O	91-93	+ +	—
91	Penta Cl.C_6-	Me	$C_9H_6Cl_5NOS$	THF-EtOH	216-18	+ + + +(19)	62(22)
92	4-Cl.C_6H_4-	Ph	$C_{14}H_{12}ClNOS$	THF-Et_2O	188-90	+ + +(24)	75(20)
93	$C_6H_5OH_2$-	Me	$C_{10}H_{13}NOS$	EtOH	93-95	+ + + +(17)	77(17)
94	$C_6H_5CH_2CH_2$-	Me	$C_{11}H_{15}NOS$	Acetone-Et_2O	106-6	—	—
95	2-Furylmethyl	Me	$C_8H_{11}NO_2S$	$CHCl_3$-hexane	77-78	—	—
96	2-Benzoxazolyl	Me	$C_{10}H_{10}N_2O_2S$	EtOH-H_2O	125-27	+ + + +(20)	47(28)
97	2-Benzthiazolyl	Me	$C_{10}H_{10}N_2OS_2$	Acetone-hexane	126-28	+ +	72
98	1-(1-Carbamoylethyl)-benzimidazol-2-yl	Me	$C_{13}H_{18}N_4O_3S$	EtOH	172-76	—	—

2998-Go was found to be comparable in effectiveness to imipramine in a limited clinical trial[11].

Experimental Procedure

Synthesis of arylthioethanamines and propanamines: Method-a—Reaction of thiophenols with ethyleneimine (propylenimine)

To a solution of **4** (34.7 g) in ethanol (300 ml) cooled in an ice-bath was added dropwise under stirring, ethylenimine (11.2 g). After being set aside for 1 hr, the solution was acidified with conc. HCl, when **27**.HCl crystallised out. Addition of ether completed the precipitation. The product was filtered off and recrystallised from aq. ethanol 30 g; m.p. 170-72°.

Method-b: Aminoalkylation of thiophenols

A solution of **4** (5 g) in 95% ethanol (50 ml) was treated with 3-chloropropyl amine hydrochloride (4.5 g) and sodium hydroxide (2.76 g) in water (5 ml). The resultant solution was heated under reflux for 1½ hr and evaporated. The residual gum was treated with water and extracted with ether. The dried ether extract was saturated with HCl gas and the precipitated salt crystallised from ethanol-ether to afford **101**.HCl; 6.4 g; m.p. 219-220° (gelling at 155°).

2-(4-*Chlorophenylthio*)-*N*,*N*-*dimethylethanamine* (**28**)

A mixture containing **27**.HCl (5 g) aq formalin (25 ml) and formic acid (25 ml) was heated under reflux overnight, the solution evaporated to dryness and the residue treated with aq $NaHCO_3$. The product was extracted into chloroform, the dried chloroform extract evaporated and the residue treated with ethanolic HCl. The gummy product became crystalline on keeping with ether and was crystallised from ethanol to give **28**.HCl; 2 g; m.p. 134-35°.

2-(4-*Chlorophenylsulphoxido*)*ethanamine* (**31**)

A solution containing **27**.HCl (5.2 g), 30% H_2O_2 (4.5 ml) and water (10 ml) was heated on a water-bath for 3½ hr. Water (10 ml) was added and the solution evaporated to dryness. The residue became crystalline and was recrystallised from EtOH to give **31**.HCl; 2.2 g; m.p. 194-95°.

2-(4-*Chlorophenylsulphonyl*)*ethanamine* (**33**)

Amine (**27**, 15 g), 30% H_2O_2 (23 ml) and water (100 ml) were heated together on a water bath for 4½ hr. The solution was evaporated to dryness and the product crystallised from ethanol 6 g of **33**.HCl; m.p. 275-77°.

N-[2-(4-*Chlorophenylthio*)*ethyl*]*guanidine* (**51**)

Amine (**27**, 5.5 g) and guanidine hemisulphate (5.5 g) in water (15 ml) were heated together under reflux for 20 hr and allowed to cool. The precipitated product was filtered off and crystallised from bioling water, after removing some insoluble material to give **51** ½ $\frac{1}{2}H_2SO_4$, (2 g); m.p. 190-91°.

N-(Phenylcarbamoyl)-1-(3-methylphenylsulphonyl)-2-propanamine (**73**)

N-(Phenylcarbamoyl)-1-(3-methylphenylthio)-2-propanamine (**70**, 2.5 g) was dissolved in acetic acid (20 ml) and treated gradually with a solution of potassium permanganate (1.5 g) in water (5 ml) below 20°. Excess permanganate was destroyed by adding saturated $NaHSO_3$ solution, the solution brought to *p*H 6 with sodium carbonate solution and extracted with chloroform. The chloroform layer was evaporated to give an oil which was purified by chromatography over alumina in $CHCl_3$. The product **73** was obtained crystalline and recrystallised from aq. ethanol; 0.8 g; m.p. 142-43°.

N-(4-Methyl-1-piperazinyl)acetyl-2-(p-chlorophenylthio)ethanamine (**54**)

Amine (**27**, 20 g) in dry acetone (20 ml) containing anhyd. K_2CO_3 (10.8 g) was treated under cooling and stirring with chloracetyl chloride (13.5 g). The product was worked up after 3 hr by evaporating the solution and washing the residue with water, and recrystallised from ethanol-ether to give the chloracetyl derivative (20 g), m.p. 188-90°. This was heated with N-methylpiperazine (30 ml) at 100° overnight. After washing with water, the product was extracted into chloroform and the extract treated with HCl gas. The dihydrochloride of **54** thus obtained was crystallised from ether-ether; 16 g; m.p. 200-205°.

Alternative syntheses of **7**: (*a*) *From ketone* **5** *by Leuckart reaction*

5 (10 g), formamide (30 ml), formic acid (4 ml) and ammonium sulphate (2 g) were heated together under reflux for 3 hr, additional formic acid (4 ml) being added at the end of first and second hour. After 24 hr, water was added and the oily product (11 g) extracted into ether. The product became crystalline with ether to afford N-formyl **7**; 4.9 g, m.p. 76-77° (Found: C, 53.2; H, 5.4; N, 5.6. $C_{10}H_{12}ClNOS$ requires C, 52.3; H, 5.3; N, 6.1%). Hydrolysis with 3*N* HCl (100 ml) under reflux for 16 hr, cooling, extraction of neutrals with ether, basification of the aqueous extract and recovery with ether gave the oily base, converted into the HCl salt (4.5 g), m.p. 151-52°, undepressed on admixture with **7**.HCl.

(*b*) *From the ketone* (**5**) *via the oxime* (**6**)

5 (6 g) and hydroxylamine HCl (2.8 g) were heated together in pyridine (5 ml) at 100° for 2 hr. The solution was poured into 3*N* HCl (100 ml) and the oily oxime extracted with ether to give **6** (6.1 g). This was dissolved in dry ether (30 ml) and the solution added to stirred LAH (2 g) in the same solvent (50 ml). The product was worked up as usual the next day and characterised as **7**.HCl (2.9 g), m.p. and m.m.p. 147-49°.

(*c*) *From tosylate* **13** *on reaction with ammonia*

5 was reduced with $NaBH_4$ to give the alcohol, m.p. 36-37°. Treatment of the alcohol (8.2 g) with *p*-toluenesulphonyl chloride (7.7 g) in pyridine (4.0 g) at 100° for 2 hr and pouring into excess dil. HCl gave the oily tosylate **13** (9 g). The tosylate (7.2 g) was heated with saturated methanolic ammonia (100 ml) in a sealed tube at 100° for 24 hr. The solution was evaporated *in vacuo* and the residue separated into a neutral part and an oily base (0.9 g). This was treated with isopropanolic HCl followed by ether. An oil separated which solidified on keeping. This was recrystallised from ethanol-ether to give **12**.HCl (0.4 g), m.p. 135-36°, undepressed on admixture with an authentic sample (see below). The supernatant deposited crystals (0.1 g), which were recrystallised to give **7**.HCl, m.p. and m.m.p. 146-48°.

(*d*) *From 4-chlorothiophenol and 2-chloropropylamine*

Commercial (±)-1-amino-2-propanol (52.5 g) was dissolved in chloroform (140 ml) and the solution saturated with HCl gas. Thionyl chloride (125 g) in chloroform (80 ml) was added slowly at room temperature during 1 hr with stirring. The solution was refluxed for 5 hr and left aside overnight. Excess ether was added to precipitate 2-chloropropylamine hydrochloride (59 g), m.p. 178-83°.

4 (14.5 g) and 2-chloropropylamine hydrochloride (15 g) were stirred together with NaOH (9 g) in water (50 ml) overnight at 30°. The basic product was extracted with ether and converted into HCl salt. Crystallisation from ethanol gave **12**.HCl (6.8 g), m.p. and m.m.p. with authentic sample (see below) 176-77°. The solid (4.5 g) obtained from the mother liquor was fractionally crystallised from EtOH-ether to give, after removal of less soluble crop, **7**.HCl (0.6 g), m.p. and m.m.p. 145-50°.

(*e*) *From* 1-(4-*chlorophenylthio*)-2-*nitropropane* (**8**)

4 (7.3 g), 30% aq formaldehyde (5 ml), nitroethane (3.75 g) and piperidine (5 drops) were heated together under reflux in ethanol (50 ml) for 16 hr. The solution was diluted with water, extracted with ether, the ether layer washed with water, dried and evaporated to give an oil (11.15 g). The oil (6 g) was chromatographed on a column of silica gel (60 g) using benzene-hexane (1 : 1) for the first 12 fractions of 50 ml each and benzene for the next 16 fractions of 50 ml. Fractions 1 and 2 on evaporation afforded bis-(4-chlorophenyl) disulphide, m.p. 72-74°. Fractions 3-5 gave the desired nitropropane (**8**, 3.5 g) as an oil, b.p. 135-45 (bath temperature)/0.5 mm; PMR ($CDCl_3$): δ 7.30 (4 aromatic Hs), 4.54 ($CH-NO_2$, *sextet*, $J = 7.5$ Hz), 3.50 ($C\begin{smallmatrix}Hs\\H\end{smallmatrix}$, $d \times d$, $J = 7.5, 14$ Hz), 3.10 ($C\begin{smallmatrix}H\\Hs\end{smallmatrix}$, $d \times d$, J

= 7.5, 14 Hz); 1.59 (CH_3, *d*, $J = 7.5$ Hz). Fractions 6-21 were mixtures and neglected. Fractions 22-24 were evaporated to give 1-(4-chlorophenylthio)-2-hydroxymethyl-2-nitropropane as an oil (1 g), b.p. 155-65° (bath temperature)/0.5 mm; PMR ($CDCl_3$): 7.30 (4 aromatic Hs); 3.9 (CH_2OH, *s*); 3.5 (CH_2-S, *s*); 3.12 (OH, *bs*), 1.57 (CH_3, *s*).

A solution of **8** (3 g) in ether (15 ml) was stirred with LAH (1.2 g) in ether (20 ml) overnight. The basic product was worked up as usual and characterised as HCl salt, (1.2 g), m.p. and m.m.p. with **7**.HCl, 145-47°.

α-Arylthiopropionamides (**10**)

A mixture of 4-chlorothiophenol (11.6 g) α-chloropropionamide (9 g), anhydrous K_2CO_3 (11.2 g) and acetone (50 ml) was heated under reflux for 16 hr and filtered. The filtrate was evaporated to dryness and the product washed with water. Crystallisation from aq ethanol gave **11** (13 g), m.p. 125-27°. Physical data for **11** and analogues are listed in Table 2.

2-(4-*Chlorophenylthio*)*propanamine* (**12**)

Amide **11** (8 g) in THF (50 ml) was added to stirred LAH (3 g) in ether (100 ml). The reaction was conducted overnight. The basic product was worked up as usual and is isolated as HCl salt. Crystallisation from ethanol gave **12**.HCl (2.3 g); m.p. 176-80° (Table 3).

1-(4-*Chlorophenoxy*)-2-*propanamine* (**15**)

4-Chlorophenoxyacetone (28 g) when heated with hydroxylamine HCl (16.8 g) in pyridine (25 ml) gave the oxime (29 g), m.p. 60-67°. Reduction of oxime (2.5 g) with LAH (1 g) gave a basic product (0.6 g) affording **15**.HCl (0.25 g), m.p. 183-85° (from EtOH-Et_2O). Alternatively the oxime (8.5 g) was hydrogenated in cyclohexane (150 ml) and ether (10 ml) with hydrogen at 100 atm. pressure and 45°, using Raney nickel (2 g) during 18 hr to give the amine (6.5 g), converted into pure **15**.HCl (4.3 g), m.p. 182-84° (from EtOH-Et_2O).

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