fluxed for 14 hr. After cooling, the mixt was washed with H_2O and extd with 10% HCl. The ext was made alk with K_2CO_3 and the oil which had sepd was extd with Et_2O. The ext was dried (K_2CO_3) and concd to dryness to give crude X as an oil. This was crystd as the oxalate. Recrystn from EtOH gave pure sample (2.8 g) as colorless prisms, mp 97–98° dec. *Anal.* ($C_{14}H_{20}N_2O_2 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H; N: calcd, 8.06; found, 7.41.

2-(*N*-Ethylamino)-*N'*-methylbenzanilide. A mixt of *N*-ethylisatoic anhydride[2] (5.75 g) and PhNHMe (3.60 g) was heated at 100° for 4 hr, at 130° for 2 hr, and at 160° for 1 hr. The mixt which crystd on cooling was recrystd from *i*-PrOH to afford pure product (5.2 g, 64%) as colorless prisms, mp 97–99°. *Anal.* ($C_{16}H_{18}N_2O$) C, H, N.

2-(*N*-Ethylchloroacetamido)-*N'*-methylbenzanilide. To a stirred mixt of 2-(*N*-ethylamino)-*N'*-methylbenzanilide (4.0 g, 0.016 mole) and anhyd K_2CO_3 (4.0 g, 0.028 mole) in PhH (130 ml) was added dropwise $ClCH_2COCl$ (2.8 g, 0.024 mole) at room temp during 10 min. The mixt was stirred at room temp for 1 hr and then washed with H_2O. The dried PhH layer was concd to dryness under reduced pressure and the crystalline residue was triturated with *i*-PrOH to afford almost pure product (4.4 g, 83%), mp 137–139°. Recrystn from *i*-PrOH gave a pure sample as colorless leaflets, mp 138–140°, nmr ($CDCl_3$) δ 1.15 (t, J = 8 Hz, 3 H), 3.23 (d, q, J = 16 Hz, 8 Hz, 1 H), 3.32 (broad s, 2 H), 3.44 (s, 3 H), 4.29 (d, q, J = 16 Hz, 8 Hz, 1 H), 6.9–7.5 (m, 9 H). *Anal.* ($C_{18}H_{19}ClN_2O_2$) C, H, N.

2-(*N*-Ethylmorpholinoacetamido)-*N'*-methylbenzanilide (XII). A soln of 2-(*N*-ethylchloroacetamido)-*N'*-methylbenzanilide (2.0 g, 0.006 mole) and morpholine (2.6 g, 0.03 mole) in PhH (30 ml) was warmed at 50° for 3 hr and then washed with H_2O. The dried PhH layer was concd to dryness under reduced pressure to give almost pure product as a colorless oil, nmr ($CDCl_3$) δ 1.13 (t, J = 7 Hz, 3 H), 2.46 (m, 4 H), 2.63 (s, 2 H), 3.19 (d, q, J = 14 Hz, 7 Hz, 1 H), 3.40 (s, 3 H), 3.65 (m, 4 H), 4.17 (d, q, J = 14 Hz, 7 Hz, 1 H), 6.9–7.5 (m, 9 H).

2-(Morpholinoacetamido)benzanilide (XI). A soln of 2-(chloroacetamido)benzanilide (5.57 g) and morpholine (4.3 g) in dioxane (180 ml) was stirred at 60–65° for 20 hr. The reaction mixt was concd under reduced pressure and the residue was poured into H_2O. The crystals were collected by filtration to give crude XI (6.9 g). Recrystn from dioxane afforded 6.2 g (94%) of XI as colorless prisms, mp 189–191°; the analytical sample melted at 190–192°. *Anal.* ($C_{19}H_{21}N_3O_3$) C, H, N. The hydrochloride was obtained as colorless needles (aqueous MeOH), mp 230–231° dec. *Anal.* ($C_{19}H_{21}N_3O_3 \cdot HCl$) C, H, N.

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Basic Ethers of 2-Anilinobenzothiazoles and 2-Anilinobenzoxazoles as Potential Antidepressants

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Some 2-[4-(β-*tert*-aminoethoxy)anilino]benzothiazoles and the corresponding benzoxazoles reversed reserpine-induced hypothermia in mice at low doses. The effects of structural variation of these molecules have been systematically examined. General pharmacology of selected compounds classifies them as antidepressants with a mild stimulant component. Anilinobenzazoles were advantageously prepared from substituted anilines and 2-chlorobenzazoles in DMF or *sym*-tetrachloroethane.

Routine pharmacological screening in these laboratories of compounds prepared for another purpose[1] revealed significant activity of 2-[4-(β-diethylaminoethoxy)phenyl]benzothiazole (**1**) in reversing reserpine-induced hypothermia in mice. This paper describes structural modifications leading to compounds having greatly increased antireserpine activity and a general pharmacological profile which suggests that they may be of value in depressive illness.

It soon became clear that in the 2-phenylbenzothiazole and 2-phenylbenzoxazole series, antireserpine activity was limited to a few basic ethers such as **1** in which a variety of substituents in the benzene ring did not greatly alter the activity. The 2'- and 3'-diethylaminoethoxy isomers of **1** were inactive, as were several 2-phenylbenzothiazoles having groups other than a basic ether in the **4'** position. The introduction of bridging groups Y (Table I) between the benzazole and Ph rings led to the considerable increase in potency of the anilino basic ether **3**, other N-containing bridging groups being less effective and those without N giving weak or inactive compds. Compd **3** has been reported to have hypocholesterolemic activity.[2] The importance of the anilino H atom is shown by the poor activity of the *N*-Me and *N*-Ac derivs **17** and **18**.

Tests on intermediates (Table II) suggested that the basic structural unit required for antireserpine activity was *p*-$ZNHC_6H_4O(CH_2)_nNR_2$ and that potency was greatly increased when Z was an electron-attracting aromatic group. When Z was *p*-nitrophenyl the diphenylamine basic ether[2] **52**, although a potent antireserpine compd, caused a severe stereotyped response in the cat (see below). Other nuclei employed as Z produced compds which, as potential antidepressants, had pharmacological profiles inferior to those of the anilinobenzazoles (*e. g.*, **3**, **14**). Since the benzimidazole **16** was almost inactive, further variations were made in the basic ethers of 2-anilinobenzothiazoles and benzoxazoles (Tables I and III).

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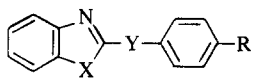
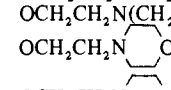
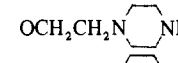
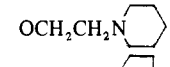
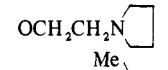
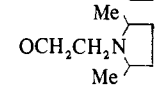
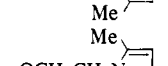
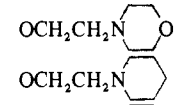
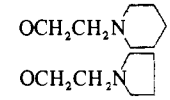
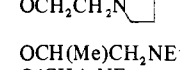
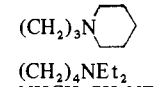
Table 1



No.	X	Y	R	Prep[a]	% yield	Mp or bp (mm), °C	Recryst[b] solvent	Formula[c]	Reserpine[d]	Cat behavior[e] Dose, mg/kg	Cat behavior[e] Intensity
1	S		$OCH_2CH_2NEt_2$	*f*					39		
2	S	O	$OCH_2CH_2NEt_2$	*g*					i		
3	S	NH	$OCH_2CH_2NEt_2$	A[h]	46	92-93	Petr (60-80°)		12.4	50	+++
4	S	SCH_2	$OCH_2CH_2NEt_2$	*g*					w		
5	S	CH_2	$OCH_2CH_2NEt_2$	D	60	95[i]	EtOH-Et_2O	$C_{22}H_{26}N_2O_5S$[i,j]	i		
6	S	$(CH_2)_2$	$OCH_2CH_2NEt_2$	*g*					51	25	i
7	S	$(CH_2)_3$	$OCH_2CH_2NEt_2$	D_1	64	101-102 dec[k]	Me_2CO	$C_{28}H_{36}N_2O_8S$[k]	i		
8	S	S	$OCH_2CH_2NEt_2$	*g*					w		
9	S	$NHCH_2$	$OCH_2CH_2NEt_2$	*g*					>50		
10	S	CH_2NH	$OCH_2CH_2NEt_2$	E_1	20	111 dec[l]	Me_2CO	$C_{20}H_{26}ClN_3OS$[l,o]	44		
11	S	NHCO	$OCH_2CH_2NEt_2$	E_2	28	254-256[l]	DMF-Et_2O	$C_{20}H_{24}ClN_3O_2S$[l,m]	25		
12	S	CONH	$OCH_2CH_2NEt_2$	E_3	87	95.5-96.5	Hex	$C_{20}H_{23}N_3O_2S$	22.5		
13	S	NHCSNH	$OCH_2CH_2NEt_2$	E_4	14	187-188	PhCl	$C_{20}H_{24}N_4OS_2$	i		
14	O	NH	$OCH_2CH_2NEt_2$	A	49	73-74	Petr (60-80°)	$C_{19}H_{23}N_3O_2$	9.8	30	+++
15	O	$(CH_2)_2$	$OCH_2CH_2NEt_2$	D_1	85	122-123[k]	MeCOEt	$C_{27}H_{34}N_2O_9$[k]	87		
16	NH	NH	$OCH_2CH_2NEt_2$	A	20	123-124	PhH-hex	$C_{19}H_{23}N_4$	w		
17	S	NMe	$OCH_2CH_2NEt_2$	A	80	Oil		$C_{20}H_{25}N_3OS$[n]	45		
18	S	NAc	$OCH_2CH_2NEt_2$	E_5	80	88-89	Petr (60-80°)	$C_{21}H_{25}N_3O_2S$	w		
19	S	NH	$OCH_2CH_2NMe_2$	B_2	50	*p*		$C_{17}H_{19}N_3OS$	33		
20	S	NH	$OCH_2CH_2NPr_2$	A	36	86.5-87.5	Petr (60-80°)	$C_{21}H_{27}N_3OS$	20		
21	S	NH	$OCH_2CH_2NBu_2$	A	41	79-80	Petr (40-60°)	$C_{23}H_{31}N_3OS$	w		
22	S	NH	$OCH_2CH_2N(CH_2Ph)_2$	A	37	103-104	EtOH	$C_{29}H_{27}N_3OS$	w		
23	S	NH	$OCH_2CH_2N(CH_2CH_2OH)_2$	B	36	101-102.5	EtOAc	$C_{19}H_{23}N_3O_3S$	w		
24	S	NH		A	50	131.5-132	EtOH	$C_{19}H_{21}N_3O_2S$	25		
25	S	NH		B	49	168-169	EtOAc	$C_{20}H_{24}N_4OS$	w		
26	S	NH		B	63[q]	138-139	EtOAc	$C_{20}H_{23}N_3OS$	3.5	35	++
27	S	NH		B_1	52	135.5-137	EtOH-H_2O	$C_{19}H_{21}N_3OS$	3.7	50	i
28	S	NH		B_1	33	115-116	EtOH-H_2O	$C_{21}H_{25}N_3OS$	8.8		
29	S	NH		E_6	70	183-184	EtOH-H_2O	$C_{21}H_{21}N_3OS$	>20		
30	S	NH	$OCH_2CH_2NH_2$	E_7	63	146.5-147.5	PhH	$C_{15}H_{15}N_3OS$	i		
31	S	NH	OCH_2CH_2NHEt	B_3	65	126-127	PhH-ligroin	$C_{17}H_{19}N_3OS$[r]	42		
32	S	NH	$OCH_2CH_2N(Et)CH_2CH_2OH$	B	40	68-70	*s*	$C_{19}H_{23}N_3O_2S$	32		
33	S	NH	$OCH_2CH_2N(Me)Et$	B_4	72	116.5-117.5	PhH-Hex	$C_{18}H_{21}N_3OS$	16		
34	S	NH	$OCH_2CH_2N(Et)Pr$	B_4	40	79-79.5	Petr (40-60°)	$C_{20}H_{25}N_3OS$	5.3	50	++
35	O	NH	$OCH_2CH_2NMe_2$	B_2	70	106.5-107	Petr (60-80°)	$C_{17}H_{19}N_2O_2$	28		
36	O	NH		B	48	160-161	EtOAc	$C_{19}H_{21}N_3O_3$	16.5		
37	O	NH		B	57	131-132	EtOAc	$C_{20}H_{23}N_3O_2$	4.1	30	++
38	O	NH		B_1	72	129-130[t]	EtOH-H_2O	$C_{19}H_{21}N_3O_2$	4.3	50 75	i ++
39	S	NH	$OCH(Me)CH_2NEt_2$	A	55	108-110	Petr (60-80°)	$C_{20}H_{25}N_3OS$	>50		
40	S	NH	$O(CH_2)_3NEt_2$	D	20	92-93	Hex	$C_{20}H_{25}N_3OS$	14.8		
41	S	NH	$O(CH_2)_4NEt_2$	A	18	86-86.5	Petr (60-80°)	$C_{21}H_{27}N_3OS$	62		
42	S	NH	$CH_2CH_2NEt_2$	A_1	16	99-100	Petr (60-80°)	$C_{19}H_{23}N_3S$	>20		
43	S	NH		B	70	103-104	Petr (60-80°)	$C_{21}H_{25}N_3S$	14	25	i
44	S	NH	$(CH_2)_4NEt_2$	A_1	40	94-95	Petr (60-80°)	$C_{21}H_{27}N_3S$	20		
45	S	NH	$NHCH_2CH_2NEt_2$	A	36	119-119.5	MeOH	$C_{19}H_{24}N_4S$	24.5		
46	S	NH	$SCH_2CH_2NEt_2$	A_1	60	81-82	PhH-petr (60-80°)	$C_{19}H_{23}N_3S_2$	w		

[a]Entries refer to general methods of prepn described in the Experimental Section. [b]Petr = petroleum ether (boiling range given), Hex = *n*-hexane. [c]Compds whose formulas are given, gave analyses for C, H, and N within 0.4% of the theoretical values unless otherwise annotated. [d]Reversal of reserpine-induced hypothermia in mice as described in ref 4. Figures denote ED_{50} mg/kg po; w = ED_{50} > 100 mg/kg; i = no activity at 100 mg/kg. Doses are calcd as the free base. [e]Cat behavior test as described in ref 4; (+) nervousness, (++) stereotyped reactions, (+++) severe stereotyped reactions. [f]Ref 19. [g]Ref 38. [h]Previously prepd by other methods, ref 2 and 38. [i]Oxalate. [j]*Anal.* H, N; C: calcd 61.4; found 60.8. [k]Citrate. [l]Hydrochloride. [m]*Anal.* C, H; N: calcd 10.3; found 9.7. [n]*Anal.* H, N; C: calcd 67.6; found 67.0. [o]*Anal.* C, H, N, Cl, S. [p]Obtd in allotropic forms, mp 138-139° (EtOAc) and mp 147-148° (EtOH), *Anal.* ($C_{17}H_{19}N_3OS$) in each case. Citrate mp 168-169° dec (MeOH). *Anal.* ($C_{23}H_{27}N_3O_8S$). [q]Also by method A_1, yield 70%. [r]*Anal.* H, N; C: calcd 65.2; found 65.9. *N,N'*-Diacetyl deriv (Ac_2O, AcOH, 100°), mp 150.5-151.5° (EtOAc). *Anal.* ($C_{21}H_{23}N_3O_3S$). [s]Purified *via* the dipicrate, mp 182-183° ($MeOCH_2CH_2OH$). The base was recovered by treatment with 2 *N* NaOH and chromatogd on alumina with PhH-$CHCl_3$, 4:1. [t]Recrystn from PhH or EtOAc gave products, mp *ca.* 116°, containing solvent which was retained at 80° (0.2 mm). Unsolvated product was recovered by recrystn from EtOH-H_2O.

Table II. *p*-ZNHC$_6$H$_4$OCH$_2$CH$_2$R^3 and Reference Compounds

No.	Z	R^3	Prep[a]	% yield	Salt	Mp or bp (mm), °C	Recryst[b] solvent	Formula[c]	Reserpine[d]	Cat behavior[e] Dose, mg/kg	Cat behavior[e] Intensity
47	H	NEt_2	*f*						20.5		
48	H	Piperidinyl	*g*	73	Base	65–67			8		
49	Et	NEt_2	E_8	64	Base	126–127 (0.05)		$C_{14}H_{24}N_2O$	32		
50	PhNHC(S)-	NEt_2	*h*						w		
51	Ph	NEt_2	D_1	44	HCl	181–182	EtOH	$C_{18}H_{25}ClN_2O$	23.5	22	+++
52	4-$NO_2C_6H_4$	NEt_2	*i*						2.8		
53	4-$MeOC_6H_4$	NEt_2	E_9	35	Citrate	106–107	MeOH–Et_2O	$C_{25}H_{34}N_2O_9$	43		
54	2-Naphthyl	NEt_2	D_1	36	Base	204–206 (0.01)		$C_{22}H_{26}N_2O$	20		
55	2-Thiazolyl	NEt_2	E_{10}	50	HCl	182–183	MeOH–Et_2O	$C_{15}H_{22}ClN_3OS$[j]	35		
56	2-Pyridyl	NEt_2	A_2	10	Base[k]	176–178 (0.05)			w		
					Dipicrate	187–188	$MeOCH_2CH_2OH$	$C_{29}H_{29}N_9O_{15}$[j,l]	>50		
57	2-Quinolyl	NEt_2	A_2	20	Base	223 (0.01)					
					Dipicrate	187–188	$MeOCH_2CH_2OH$	$C_{35}H_{31}N_9O_{15}$	i		
58	2-Btz-NH$(CH_2)_3$OCH$_2$CH$_2$NEt$_2$[m]		E_{11}	44		Oil[k]		$C_{16}H_{25}N_3OS$	6.2		
Imipramine[n]									2.0		
Nortriptyline[n]									0.6	5	+++
dl-Amphetamine[o]											

[a–e] As in Table I. [f] Ref 22. [g] See Experimental Section under intermediates. [h] Ref 24. [i] Ref 2. [j] *Anal.* C, H, Cl. [k] See Experimental Section. [l] *Anal.* H, N; C: calcd 46.9; found 47.5. [m] 2-Btz = 2-benzothiazolyl. [n] As HCl. [o] As sulphate.

The greatest changes in antireserpine activity resulted from varying the terminal basic group (*cf.* Tables I and III). By comparison with the diethylamino compd **3**, activity was reduced with other dialkylamino groups except NEtPr, **34**, but potent compds were obtained when NR_2 was a piperidine or pyrrolidine ring (*e. g.*, **26**, **27**). The optimum chain length resulted when $n = 2$ in the general structure above and replacement of the ether oxygen by CH_2, NH, or S (**43**, **45**, **46**) gave less active compds.

Benzene ring substitution (Table III) in most cases reduced the activity, but some increase resulted with a Me or MeO group in the 5 position (**63**, **64**) when the terminal group was NEt_2. Also the reduction in activity resulting from 5-Cl or 5-CF_3 substitution (**62**, **66**, **71**) suggests that the electronic nature of substituents in the 5 position influences the activity. In the diphenylamines **52** and **53**, however, the effects are different since the electron-attracting NO_2 group gives the more active compd.

The pharmacological properties of selected anilinobenzazoles resembled those of imipramine and other tricyclic antidepressants in several respects, but they had a much weaker anticholinergic effect and showed little depressant activity. Their actions included a mild stimulant component, suggesting antidepressant properties intermediate between those of imipramine and amphetamine. The anilinobenzazoles were very similar pharmacologically to a previously reported series of phenacylmercaptoimidazolines,[3] although there is no obvious structural relationship between the two series. In both series some compds at a relatively high dose caused amphetamine-like behavioral changes in cats, ranging from nervousness to stereotyped reactions, as previously described,[4] but some members of the present series (*e. g.*, **27**, **38**, and **79**) had no effect or caused only mild stereotypy and the ratios of the CNS-stimulant dose to the antireserpine ED_{50} were as good as or superior to those of the imidazolines.

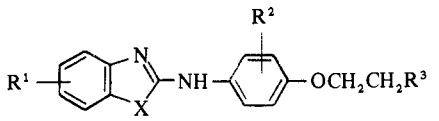
The benzoxazoles **14** and **38** were teratogenic in rats, but the closely related benzothiazoles **27** and **79** have not shown this property although extended tests remain to be carried out.

The pharmacological results are given in more detail in the Experimental Section.

Chemistry. The preparation of anilinobenzazoles by reaction between a 2-halogenobenzazole and a substituted aniline[5,6] proved more generally useful when DMF or $(Cl_2CH)_2$ was used as solvent. Use of DMF gave rise to variable amounts of the 2-dimethylaminobenzazoles, making purification of some products more difficult. 2-Chlorobenzothiazole gave a 65% yield of the 2-Me_2N deriv after 5-hr boiling in DMF which was initially freed of Me_2NH. The surprisingly good results with $(Cl_2CH)_2$ may be due to a catalytic effect of the HCl produced by decompn of the solvent, which could further activate the benzazole halogen by salt formation.[7] This view was supported by the reactivity of the crystalline BF_3 salt of 2-chlorobenzoxazole, which gave a 64% yield of 2-[**4**-(β-chloroethoxy)anilino]benzoxazole, at the bp of CH_2Cl_2, although this type of reaction was too variable to be of general use. Comparative results using DMF or $Cl_2CHCHCl_2$ were only obtained in a few cases and the solvent used is not necessarily that of choice; $(Cl_2CH)_2$ seemed superior for anilines lacking a second basic group.

Because of difficulties experienced in the preparation of 2-chlorobenzoxazoles from 2-mercaptobenzoxazoles, direct treatment of the latter with anilines[8] was preferred in spite of the necessity for chromatography of the products.

Table III



No.	R^1	X	R^2	R^3	Prep[a]	% yield	Mp, °C	Recryst[b] solvent	Formula[c]	Reserpine[d]	Cat behavior[e] Dose, mg/kg	Cat behavior[e] Intensity
59	4-Cl	S	H	NEt_2	A	57	104.5-105.5	PhH-petr (60-80°)	$C_{19}H_{22}ClN_3OS$[f]	62		
60	4-Me	S	H	NEt_2	A_1	25	92-93	Petr (60-80°)	$C_{20}H_{25}N_3OS$	21	25	±
61	4-MeO	S	H	NEt_2	A	15	118-119	Petr (80-100°)	$C_{20}H_{25}N_3O_2S$	23	25	+
62	5-Cl	S	H	NEt_2	A	60	179.5-180.5	PhH-petr (60-80°)	$C_{19}H_{22}ClN_3OS$	27		
63	5-Me	S	H	NEt_2	A	35	141-142	Petr (80-100°)	$C_{20}H_{25}N_3OS$	10.1	25	±
64	5-MeO	S	H	NEt_2	C	10	163-164	EtOH-H_2O	$C_{20}H_{25}N_3O_2S$	4.2	75	+
65	5-NO_2	S	H	NEt_2	A_1	30	149-150	MeOH	$C_{19}H_{22}N_4O_3S$	w		
66	5-CF_3	S	H	NEt_2	A	60	186-186.5	Petr (100-120°)	$C_{20}H_{22}F_3N_3OS$	>50		
67	5-AcNH	S	H	NEt_2	A_1	20	202-203	PhH	$C_{21}H_{26}N_4O_2S$	i		
68	6-Cl	S	H	NEt_2	A	54	106-107	PhH-petr (60-80°)	$C_{19}H_{22}ClN_3OS$	12.6	25	+
69	6-Me	S	H	NEt_2	A	35	88-89	Petr (60-80°)	$C_{20}H_{25}N_3OS$	10.7	25	+
70	6-NO_2	S	H	NEt_2	A	75	170-170.5	EtOH	$C_{19}H_{22}N_4O_3S$[g]	23.2		
71	5-Cl	O	H	NEt_2	A_1	55	117-118	PhH-Hex	$C_{19}H_{22}ClN_3O_2$	14.5	25	-
72	5-Me	O	H	NEt_2	C	42	106-107	Petr (100-120°)	$C_{20}H_{25}N_3O_2$	5.4	50	±
73	5-$PhCH_2O$	O	H	NEt_2	C	32	120.5-121	Petr (100-120°)	$C_{26}H_{29}N_3O_3$	w	50	+
74	6-Cl	O	H	NEt_2	C	40	100-101	Hex	$C_{19}H_{22}ClN_3O_2$	13	25	±
75	6-Me	O	H	NEt_2	C	29	97-98	PhH	$C_{20}H_{25}N_3O_2$	16	20	+
76	6-NO_2	O	H	NEt_2	C_1	40	160-160.5	PhH	$C_{19}H_{22}N_4O_4$	28		
77	5-Me	S	H	Pyrrolidinyl	A	14	153-154	EtOH-H_2O	$C_{20}H_{23}N_3OS$	3.5	50	++
78	5-Me	O	H	Pyrrolidinyl	C	43	144-145	PhH	$C_{20}H_{23}N_3O_2$	2.3	50	++
79	5-MeO	S	H	Pyrrolidinyl	B_1	80	167-167.5	PhH	$C_{20}H_{23}N_3O_2S$	3.1	50	+
80	6-Cl	S	H	Piperidinyl	A	25	148-149	EtOH	$C_{19}H_{22}ClN_3OS$	13		
81	6-MeO	S	H	Piperidinyl	B	55	118-119	EtOH-H_2O	$C_{21}H_{25}N_3O_2S$	8.6		
82	6-Cl-5-MeO	S	H	Piperidinyl	B_1	68	177-178	PhH	$C_{21}H_{24}N_3O_2S$	>20		
83	5,6-Me_2	O	H	Piperidinyl	A_1	50	142-144	EtOAc	$C_{22}H_{27}N_3O_2$	7.7		
84	H	S	2'-Me	NEt_2	D	20	113-114	Petr (60-80°)	$C_{20}H_{25}N_3OS$[h]	>50	20	-
85	H	S	3'-Cl	NEt_2	A_1	55	114-115	PhH-petr (60-80°)	$C_{19}H_{22}ClN_3OS$[i]	41		
86	H	S	3'-5'-Me_2	NEt_2	A_1	60	Liq[j]		$C_{21}H_{27}N_3OS$	21		
87	H	S	2'-Me-5'-*i*-Pr	NEt_2	A_1	40	134.5-135.5	Petr (60-80°)	$C_{23}H_{31}N_3OS$	i		

[a-e] As in Table I. [f] *Anal.* H, N; C: calcd 60.7; found 60.2. [g] *Anal.* C, H, S; N: calcd 14.5; found 14.0. [h] *Anal.* C, N; H: calcd 7.1; found 7.55. [i] *Anal.* C, H, N, Cl. [j] Purified by chromatog on alumina (5% EtOH in Et_2O).

The reaction between 2-mercapto-5-methoxybenzothiazole and SO_2Cl_2[9] even at 0° gave a dichloro compd assumed to be the 2,6-dichloro-5-methoxy deriv. The reactivity of the 2-chlorobenzazoles toward anilines was qualitatively similar to that with alkoxide ions[10] in that 5- or 6-OMe substituents were deactivating and 5- or 6-NO_2 were activating.

Other products and intermediates were obtained by adaptation of standard procedures as given in the Experimental Section.

Experimental Section

Pharmacology. Compds were administered orally either as soluble salts or in 0.5% tragacanth suspension in the mouse and rat tests, control animals receiving the vehicle alone. In the cat behavior study[4] compds were given orally in gelatine capsules. Doses are expressed as the free base. All compds were screened by the reserpine hypothermia test in mice as previously described[4] and cat behavior was studied on selected compounds. The results are given in the tables.

More detailed pharmacological study was carried out on compds 3, 14, 26, 37, 38, and 79 and more particularly on 38 and 79. Both 38 and 79 showed properties in common with those of tricyclic antidepressants in that they antagonized an established reserpine hypothermia, prevented tetrabenazine sedation in the rat, inducing instead a compulsive motor activity[11] at 20-25 mg/kg and enhanced the agonist effects of norepinephrine on the isolated rat vas deferens.[12] Neither compd potentiated tryptamine convulsions in mice[13] and therefore did not appear to inhibit MAO, but both, like imipramine, potentiated the stimulant effect of dopa in mice in which MAO was partially inhibited by iproniazid.[14] The anticholinergic and antihistaminic properties of 38 and 79 were weaker than those of imipramine as assessed by ACh-induced chromodacryorrhoea in rats and on the isolated guinea pig ileum. Compd 38 showed a marked antagonism of an established tremorine hypothermia but less effect against tremor and 79 behaved similarly against oxotremorine, both compds resembling imipramine in this respect.[15] Neither 38 nor 79 affected normal rectal temp nor prevented nor reversed chlorpromazine hypothermia in mice. No analeptic activity was evident against pentobarbital lethality in mice. Both substances antagonized maximal pentylenetetrazole[16] and electroshock convulsions[17] in mice (ED_{50} = 54-70 mg/kg). Against phenylquinone writhing in mice the ED_{50} was 5-8 mg/kg but no other analgetic or antiinflammatory properties were detected. Mild anorexia occurred in rats[4] at 25-50 mg/kg.

The acute LD_{50} in mice was 670-680 mg/kg, the minimal convulsant dose being 400-500 mg/kg. The compds differed from imipramine in causing a state of alertness and increased sensitivity. In rodents this appeared at doses of 50-100 mg/kg following a brief depressed period and in cats and dogs nervousness or slight stereotyped reactions occurred at 50-75 mg/kg. In single squirrel monkeys, 10 or 25 mg/kg of 38 caused a slight increase in motor activity; at 40 mg/kg the monkey showed a tendency to look around with jerky head movements. In the baboon, 20 mg/kg of 79 caused a slight increase in motor activity.

Repeat dosing of 38 in rats for 14 days at 10, 30, or 100 mg/kg per day caused a significantly reduced body wt gain at 30 and 100 mg and a significantly increased adrenal wt in the female rats at the 100-mg dose. In dogs, 5 mg/kg per day for 6 months had no effect whereas 10 mg/kg per day caused a slight uneasiness and reduction in appetite, and 15 and 45 mg/kg per day caused some fear, quietness, confusion, stereotyped reaction, anorexia, and reduction in wt gain. At 45 mg/kg per day the liver, thymus, and adrenals were significantly increased, and the pancreas significantly decreased, in wt. The hematological profile was not altered at any dose level in either species.

In teratogenic tests in rats 38 given at 25 or 50 mg/kg per day on days 0-19 of pregnancy or 60 mg/kg per day on days 5-15, caused malformations in 4, 33, and 27% of fetuses, resp; the malformations affected mainly the ribs, which were "wavy", and the

sternebrae, which were often bifurcated. There was a general lack of ossification of the skull, vertebrae, sternebrae, ribs, and forelimbs. In New Zealand White rabbits, 38 at 20, 40, and 60 mg/kg per day on days 0–28 caused abnormalities in 3, 5, and 62% of fetuses, respectively, mainly in the form of absent or malformed phalanges of the paws. In the rat and rabbit tests however, the 50 and 60 mg/kg doses caused behavioral effects, anorexia, and depressed body wt increase in the mothers.

Compd 14 was shown to be markedly teratogenic in rats, causing 42% abnormalities at 60 mg/kg per day on days 5–15 whereas the benzothiazole 27 showed no definite evidence of teratogenicity at 15, 30, and 60 mg/kg per day, suggesting that this effect may be associated with the benzoxazole nucleus. Also, the benzothiazole 79 showed no gross teratogenic effects when given at 25 and 50 mg/kg per day; results of the examination of the skeletons are not available.

Chemistry. Mps were detd in capillary tubes in a Büchi apparatus and are corrected. Chromatog materials were alumina type H (Spence) deactivated by addn of 5% w/w of 10% HOAc and silica for chromatography (Merck), 0.2–0.5 mm, solvents quoted are those which elute the required product from the column. Petr = petroleum ether (boiling range given). Solvent exts of aqueous mixts were washed (H_2O), dried ($MgSO_4$), and evapd at 40–50° (*ca.* 20 mm) unless stated otherwise. Where analyses are indicated only by symbols of the elements analytical results for those elements were within ±0.4% of the theoretical values; compds for which only formulas are given were analyzed for C, H, and N. Ir and uv spectra were consistent with the structures assigned.

General Methods of Preparation. A. A soln of a 2-chlorobenzazole (or for 59, 2-bromo-4-chlorobenzothiazole[18]) (0.05 mole) and a substituted aniline (0.05 mole) in DMF (40 ml) was boiled under reflux for 6 hr under N_2. The soln was dild with 2 *N* HCl and washed with Et_2O. The acid soln was basified (NaOH soln) and the product was isolated by Et_2O extn and purified if necessary by chromatography on alumina with PhH or Et_2O.

A_1. The reactants as in A and $Cl_2CHCHCl_2$ (80 ml) were boiled under reflux for 4 hr, concd at reduced pressure, and worked up as in A.

A_2. 4-(β-Diethylaminoethoxy)aniline (0.1 mole) and 2-bromopyridine or 2-bromoquinoline (0.1 mole) were heated at 200° for 6 hr, cooled, and worked up as in A. The products were dist using a 15-cm Vigreux column. The anilinopyridine 56 was purified *via* its dipicrate (Table II) from which the base was recovered by decompn with 40% NaOH soln.

B. A soln of a 2-[4-(ω-chloroalkoxy)anilino]benzazole or a 2-[4-(ω-chloroalkyl)anilino]benzazole (0.1 mole) and an amine (0.3 mole) in PhMe (300 ml) were boiled under reflux for 16 hr. The soln was extd with 2 *N* HCl and the acid ext was basified with 10 *N* NaOH. The product was isolated by Et_2O extn and, if necessary, was chromatogd on alumina with $CHCl_3$.

B_1. The reactants of method B in $MeOCH_2CH_2OH$ (150 ml) were boiled under reflux for 1 hr. The soln was evapd at reduced pressure and the residue was worked up as in method B.

B_2. A 2-[4-(ω-chloroalkoxy)anilino]benzazole (0.01 mole), an amine (0.03 mole), EtCOMe (30 ml), and NaI (0.2 g) were heated in a sealed tube at 90° for 16 hr. The mixt was evapd and worked up as in method B.

B_3. A 2-[4-(ω-chloroalkoxy)anilino]benzazole (0.01 mole) and a large excess of an amine were heated in a sealed tube at 120° for 4 hr, evapd, and worked up as in B.

B_4. As in B_3 but with the addn of NaI (50 mg) and DMF (15 ml).

C. A 2-mercaptobenzoxazole (0.01 mole), a substituted aniline (0.01 mole), and *o*-dichlorobenzene (15 ml) were boiled under reflux for 16 hr. The soln was extd with 2 *N* HCl, the acid ext was basified with 10 *N* NaOH, and the product, obtd by EtOAc extn, was purified by chromatog, first on silica with Me_2CO and then on alumina with $CHCl_3$.

C_1. As described in method C but using $Cl_2CHCHCl_2$ as solvent.

D. An appropriate phenol in acetone with anhyd K_2CO_3 was alkylated with a diethylaminoalkyl chloride.[19]

D_1. As in D but using EtOH–NaOEt as the medium.[19]

Miscellaneous Methods. E_1. 2-Chloromethylbenzothiazole (0.01 mole) and 4-(β-diethylaminoethoxy)aniline (0.01 mole) in xylene (50 ml) were boiled under reflux for 18 hr and cooled, and the gummy ppt was extd with hot Me_2CO to obtain the HCl salt, which crystd from the ext.

E_2. 2-Aminobenzothiazole (1.1 g) in pyridine (50 ml) was aroylated with 4-(β-diethylaminoethoxy)benzoyl chloride[20] in the usual way and the soln was evapd to obtain the crude HCl salt.

E_3. 4-(β-Diethylaminoethoxy)aniline reacted with benzo-1,4-thiazine-2,3-dione in HOAc as described using aniline.[21] The soln was evapd, dild with H_2O, and basified. The product was isolated by EtOAc extn and purified by chromatog on alumina (PhH–hexane, 3:1).

E_4. 4-(β-Diethylaminoethoxy)phenyl isothiocyanate[4] (0.05 mole) and 2-aminobenzothiazole (0.05 mole) were heated at 100° for 5 hr. The product crystd on trituration with CH_3CN.

E_5. Compd 3 (1 g) was heated with Ac_2O (3 ml) for 3 hr at 100°, the mixt was poured into H_2O, made alk with NH_4OH, and extd with Et_2O.

E_6. 2-[4-(β-Aminoethoxy)anilino]benzothiazole (30) (0.57 g), hexane-2,5-dione (0.5 g), EtOH (20 ml), EtOAc (20 ml), and HOAc (1 drop) were boiled for 3 hr under reflux and evapd.

E_7. A soln of 2-[4-(β-azidoethoxy)anilino]benzothiazole (3.8 g) in THF (125 ml) was added to LAH (6 g) in Et_2O (200 ml) and boiled for 2 hr. The usual work-up gave a solid which was easily distinguishable from the starting azide by its ir spectrum.

E_8. 4-(β-Diethylaminoethoxy)acetanilide[22] (0.03 mole) was reduced with LAH (0.06 mole) in Et_2O with 1.5-hr boiling.

E_9. A soln of 4-hydroxy-4′-methoxydiphenylamine[23] (5 g) in HOAc (25 ml) and Ac_2O (25 ml) was allowed to stand overnight and poured into H_2O to give the *N*-Ac deriv (5.9 g); mp 160–165°. This was added to a stirred suspension of NaH (1.06 g) in DMF (100 ml) followed after 5 min by a soln of β-diethylaminoethyl chloride · HCl (3.8 g) in DMF (50 ml) and the mixt was stirred at 95° for 5 hr. The solvent was evapd and the residue was mixed with 2 *N* NaOH and Et_2O. The product from the Et_2O layer (6.4 g, brown oil) was boiled with 5 *N* HCl (150 ml; 16 hr) and the basic ether was isolated in the usual way and dist (4.7 g): bp 202–204° (0.01 mm).

E_{10}. 4-(β-Diethylaminoethoxy)phenylthiourea[24] (1.44 g), $ClCH_2CH(OEt)_2$ (0.82 g), 2 *N* H_2SO_4 (5 ml), and EtOH (20 ml) were boiled for 3 hr under reflux, the EtOH was evapd, and the residue was shaken with 2 *N* NaOH and Et_2O. The product in the Et_2O layer was extd into 2 *N* HCl, basified, isolated by Et_2O extn, and dist (1 g): bp 205–206° (0.1 mm). The hydrochloride was obtained by evapn of a 1 *N* HCl soln of the base.

E_{11}. Use of 3-(β-diethylaminoethoxy)propylamine[25] in method A and purification by chromatog on alumina [PhH–petr (60–80°) 1:1] gave the product as a colorless oil.

Intermediates. Substituted Anilines Used in Methods A, A_1, and A_2. 4-(β-Tosyloxy)ethoxyacetanilide reacted with amines as previously reported[4] to give the following *p*-$XCH_2CH_2OC_6H_4NH_2$: X = NPr_2, 79%, bp 170–172 (4 mm), di-HCl mp 201–202 dec (EtOH–H_2O) [*Anal.* ($C_{14}H_{26}Cl_2N_2O$)]; X = piperidino, 73%, bp 159–161° (0.2 mm), mp 65–67° (lit.[22] mp 65–66.5); X = morpholino, 54%, bp 144–150° (0.005 mm), mp 71–73° (lit.[22] mp 69.5–70.5°); X = 4-methylpiperazino, 43%, bp 149–152° (0.02 mm), mp 44–48°; picrate (using 1 equiv of picric acid), mp 137.5–138° (MeOH) [*Anal.* ($C_{20}H_{24}N_6O_8$)]; X = $N(CH_2Ph)_2$, 60%, bp 199–203° (0.05 mm) (lit.[26] bp 191–193° (0.02 mm)).

4-(δ-Diethylaminobutyloxy)aniline. 4-Acetamidophenol and $Br(CH_2)_4Br$ (3 equiv) under conditions D_1 gave 4-(δ-bromobutyloxy)-acetanilide (45%, mp 100–102° from Me_2CO–hexane). *Anal.* ($C_{12}H_{16}BrNO_2$) C, H, Br. This product reacted with Et_2NH under the conditions B_2 to give 4-(δ-diethylaminobutyloxy)acetanilide (HCl mp 134–136°, EtOH–Et_2O) which was hydrolyzed (6 *N* HCl, 3-hr boiling) to the required aniline (yield 22% overall): bp 128–130° (0.01 mm). *Anal.* ($C_{14}H_{24}N_2O$).

4-(3-Chloropropyl)aniline was obtd by hydrogenation (10% Pd/C, EtOH, 1 atm) of the NO_2 compd[4] as an oil: bp 127–128° (1 mm), di-HCl mp 218–219° (lit.[27] mp 195.5–196.5°).

4-(β-Diethylaminoethylamino)aniline was similarly obtd (Pt, EtOH, 3 atm) as an oil, bp 120–121° (0.05 mm under N_2), which deteriorated in air.

3-Chloro-4-(β-diethylaminoethoxy)aniline. The NO_2 compd[28] was reduced with $SnCl_2$–concd HCl (2 hr, 100°), the mixt was heated with 10 *N* NaOH for 1 hr at 100° to decomp the Sn complex, and the aniline was isolated by Et_2O extn and dist (75%): bp 151–152° (1 mm), mp 41–42°. *Anal.* ($C_{12}H_{19}ClN_2O$) C, H, N, Cl.

4-(β-Diethylaminoethoxy)-3,5-dimethylaniline. 4-(β-Diethylaminoethoxy)-3,5-dimethylnitrobenzene was obtd by method D (63%): bp 164–165° (1 mm), citrate mp 167–168° (MeOH). *Anal.* ($C_{20}H_{30}N_2O_{10}$). Hydrogenation of the base (10% Pd/C, EtOH, 1 atm) gave the aniline (95%): bp 145–146° (0.8 mm), dioxalate mp 165–166° (MeOH–Et_2O). *Anal.* ($C_{18}H_{28}N_2O_9$) H; C: calcd, 51.9; N: calcd, 6.7; found, C, 51.3; N, 7.3.

4-(β-Diethylaminoethoxy)-5-isopropyl-2-methylaniline. 4-Acetamidothymol was alkylated by method D to give 4-(β-diethylaminoethoxy)-5-isopropyl-2-methylacetanilide (27%): mp 86–87° [petr

(60–80°)]. *Anal.* ($C_{18}H_{30}N_2O_2$) C, H; 40% of the starting material was recovered. The basic ether was boiled for 1 hr with 6 *N* HCl to give the aniline as an oil (yield 95%) suitable for the next stage. Distn under N_2 gave a colorless oil: bp 127–128° (0.8 mm). *Anal.* ($C_{16}H_{28}N_2O$).

ω-Chloroalkoxy (or ω-Chloroalkyl)anilinobenzazoles for Methods B–B_4. A 2-chlorobenzazole (0.02 mole), a 4-(ω-chloroalkoxy)- or 4-(ω-chloroalkyl)aniline (0.02 mole), and $Cl_2CHCHCl_2$ (60 ml) were boiled under reflux for 3 hr, cooled, dild with $CHCl_3$ (30 ml), and washed successively with H_2O, $NaHCO_3$ soln, and H_2O. During the washing some of the product sepd and was filtd off. The organic phase was evapd and more product was obtd by recrystn of the residue. Thus were obtd: 2-[4-(β-chloroethoxy)anilino]benzothiazole (85%), mp 173–174° [PhH–petr (60–80°)] [*Anal.* ($C_{15}H_{13}ClN_2OS$)]; 2-[4-(β-chloroethoxy)anilino]benzoxazole (80%), mp 165–167° (PhH) [*Anal.* ($C_{15}H_{13}ClN_2O_2$)]; 2-[4-(3-chloropropyl)anilino]benzothiazole (55%), mp 121–123° [PhH–petr (60–80°)]. [*Anal.* ($C_{16}H_{15}ClN_2S$) C, H, N, Cl]; 2-[4-(β-chloroethoxy)anilino]-6-methoxybenzothiazole (53%), mp 146–147° [PhH–petr (60–80°) and EtOH–H_2O] [*Anal.* ($C_{16}H_{15}ClN_2O_2S$) C, H, N, Cl]; 6-chloro-2-[4-(β-chloroethoxy)anilino]-5-methoxybenzothiazole (30%), mp 177–178° [PhH–petr (60–80°)] [*Anal.* ($C_{16}H_{14}Cl_2N_2O_2S$) H, N; C: calcd, 52.05; found 52.5].

2-[4-(β-Chloroethoxy)anilino]-5-methoxybenzothiazole. 5-Methoxy-2-methylsulfonylbenzothiazole[29] (1105 g), 4-(β-chloroethoxy)aniline (780 g), and PhMe (5 l.) were boiled under reflux using a water trap. After 2 hr a further 156 g of the aniline was added and boiling was continued for 4 hr. The product was filtd off when cool and was washed with EtOH (3 l.) to give 1290 g (85%), mp 176–178°, which was used for the next stage. Recrystn from $CHCl_3$ gave mp 183–184°. *Anal.* ($C_{16}H_{15}ClN_2O_2S$).

2-Mercaptobenzoxazoles were prepd from 2-aminophenols by a reported method[30] to give: 2-mercapto-6-methylbenzoxazole (75%), mp 211–212° (EtOH–H_2O) [*Anal.* (C_8H_7NOS)]; 2-mercapto-5-methylbenzoxazole (73%), mp 221–222° (lit.[31] mp 216–217°); 5,6-dimethyl-2-mercaptobenzoxazole (65%), mp 219–220° (EtOH) [*Anal.* (C_9H_9NOS)].

2-Mercapto-5-trifluoromethylbenzothiazole. Bis(2-nitro-4-trifluoromethylphenyl)disulfide[32] (72 g), H_2O (2 l.), concd HCl (45 ml), and reduced Fe powder (100 g) were stirred at 80° for 2 hr, allowed to stand overnight, made basic with NaOH soln, washed with Et_2O, and filtd. The filtrate was acidified with HOAc and the product was isolated by Et_2O extn and distd to give 2-amino-4-trifluoromethylbenzenethiol (40%): bp 76–78° (2 mm) [lit.[33] bp 76–78° (2 mm)]. The aminothiol and CS_2 under the usual conditions[34] gave 2-mercapto-5-trifluoromethylbenzothiazole (78%): mp 222–224° (EtOH–H_2O and HOAc). *Anal.* ($C_8H_4F_3NS_2$).

2-Chlorobenzothiazoles and benzoxazoles. 2-Aminobenzothiazoles were treated with HNO_2 and Cu under described condns[35] to yield: 2-chloro-4-methylbenzothiazole (45%), mp 40–43° (lit.[36] mp 42–43°) and 2-chloro-4-methoxybenzothiazole (40%), mp 67–69° [petr (60–80°)]. *Anal.* (C_8H_6ClNOS) C, H, N, Cl.

5-Acetamido-2-chlorobenzothiazole. 2-Chloro-5-nitrobenzothiazole[10] (6.5 g) was added portionwise during 40 min to a stirred, boiling mixt of EtOH (45 ml), HOAc (3 ml), and Fe powder (15 g). After a further 1 hr, EtOH (60 ml) and charcoal were added, the mixt was boiled for 15 min and filtd and the residue was extd with hot EtOH. The combined liquors were dild with 500 ml of H_2O and after 2 days at 5° the 5-amino-2-chlorobenzothiazole was collected and recrystd from PhH (2.1 g): mp 145–150°. The amine was acetylated (AcCl, pyridine) to give the title compd (2.0 g): mp 169–170° (PhH). *Anal.* ($C_9H_7ClN_2OS$) C, H, N, Cl.

2,6-Dichloro-5-methoxybenzothiazole. 2-Mercapto-5-methoxybenzothiazole with SO_2Cl_2 under condns reported to give the 2-chloro analog,[9] gave only a dichloro deriv: mp 128–129° [petr (60–80°)]. *Anal.* ($C_8H_5Cl_2NOS$).

2-Chloro-5-trifluoromethylbenzothiazole was prepd from the 2-mercapto compd in the usual way[9] and purified by recrystn (MeOH) and sublimation at 60° (0.1 mm): yield 71%, mp 60–61°. *Anal.* ($C_8H_3ClF_3NS$) C, H, N, Cl.

2-Chloro-5,6-dimethylbenzoxazole. 5,6-Dimethyl-2-mercaptobenzoxazole (6 g) was added portionwise to a stirred soln of $COCl_2$ (4 g) in $CHCl_3$ (14 ml) with DMF (2 drops) at 0°, stirred for 1 hr then set aside overnight. The soln was boiled under reflux with slow passage of $COCl_2$ for 7 hr and evapd and the oil extd with petr 40–60°. The yellow product [4 g, mp 76–77° from hexane; *Anal.* (C_9H_8ClNO) Calcd: C, 59.5, H, 4.4; found, C, 59.15, H, 5.3] was sensitive to atm moisture, giving 5,6-dimethylbenzoxazolone:[37] mp 177°

Phenols Used in Method D. 2-(*p*-Hydroxyphenylalkyl)benzothiazoles and benzoxazoles were obtd by a described procedure[38] from *p*-methoxyphenylalkanoic acid chlorides and *o*-aminothiophenol or *o*-aminophenol, respectively, and demethylation of the intermediate MeO compds with pyridine · HCl,[19] giving the following compds: 2-(*p*-hydroxyphenethyl)benzoxazole (48%), mp 110–111° (EtOH); 2-(*p*-hydroxybenzyl)benzothiazole (54% overall), mp 168° (EtOH–H_2O); 2-[3-(*p*-methoxyphenyl)propyl]benzothiazole (80%), mp 74.5–75.5° (hexane) [*Anal.* ($C_{17}H_{17}NOS$)]; 2-[3-(*p*-hydroxyphenyl)propyl]benzothiazole (58%), mp 130° (PhH) [*Anal.* ($C_{16}H_{15}NOS$)].

2-(*p*-Hydroxyanilino)benzothiazoles were obtd by using a *p*-aminophenol in method A above and neutralizing the HCl soln with $NaHCO_3$. In this way 2-(*p*-hydroxyanilino)benzothiazole was pptd (85%): mp 205–206° (lit.[19] mp 203–204°) and 2-(4-hydroxy-2-methylanilino)benzothiazole was isolated by EtOAc extn (45%): mp 207–208° (MeOH–H_2O). *Anal.* ($C_{14}H_{12}N_2OS$).

2-[4-(β-Azidoethoxy)anilino]benzothiazole. A soln of 2-[4-(β-chloroethoxy)anilino]benzothiazole (6.4 g) in DMF (35 ml) was added during 1 hr to a stirred suspension of NaN_3 (5.5 g) in DMF (50 ml) at 95°. After a further 21 hr the soln was concd to half vol and dild with H_2O (150 ml), and the ppt was recrystd from PhH to give 5.45 g (85%): mp 147–148.5°. *Anal.* ($C_{15}H_{13}N_5OS$).

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Diuretics. 1. 1-Imidoyl-2-(2- and 3-indolyl)indolines

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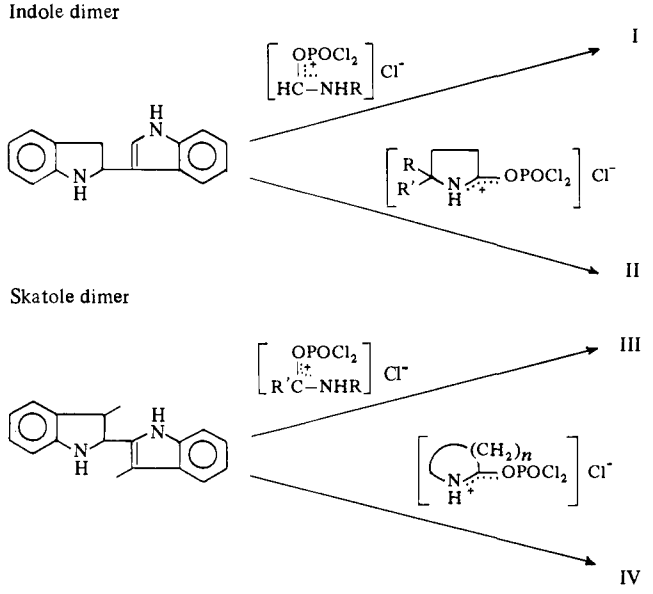
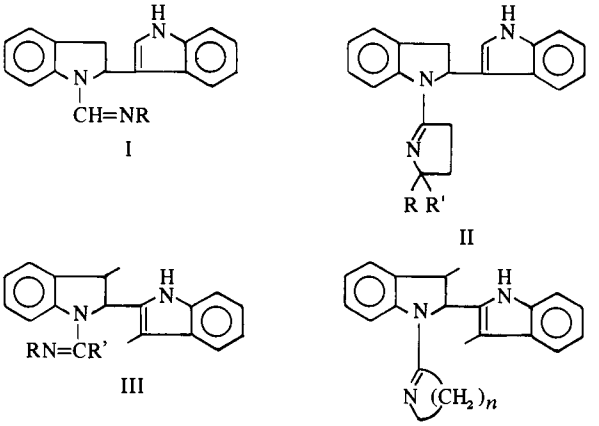
A series of 1-imidoyl-2-(2- and 3-indolyl)indolines was synthesized and evaluated for diuretic activity. The compounds were generally prepared by treating various dimers of indoles with carboxamide-$POCl_3$ adducts. Several 2,3,5,6-tetrahydro-5-(3-indolyl)-1*H*-pyrrolo[2,1-*b*][1,3]benzodiazepines were obtained by a rearrangement reaction. A discussion of structure-activity relationships is presented.

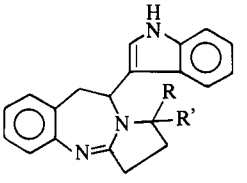
Intensive synthetic work on oral diuretics in the past 2 decades has resulted in several efficient agents exemplified by chlorothiazide,[1] ethacrynic acid,[2] furosemide,[3] spironolactone,[4] and triamterene.[5] In spite of the apparent commercial success of these agents, a totally satisfactory diuretic agent has not been attained. In his address for the Third Award in Medicinal Chemistry, Sprague[6] clearly indicated the necessity for continuous effort of medicinal chemists in this field.

We wish to report a new chemical class of oral diuretics represented by structures I-V.† Preliminary pharmacological evaluation has been encouraging in view of selective saluretic, K^+ sparing responses elicited by these compounds. This paper deals with chemical syntheses, biological screening results, and structure-activity relationships of the series.

Chemistry. Compounds I-IV were prepared by treating various dimers of indoles with appropriate carboxamide-$POCl_3$ adducts.[7]







36, R, R' = H
37, R = H; R' = CH_3
38, R, R' = CH_3

Dimerization of Indoles. Indoles are known to dimerize and trimerize in the presence of a protonic acid. The chemistry of this polymerization has been reviewed.[8]

By choosing an appropriate solvent as the reaction medium, we were able to dimerize several indoles with minimal concurrent trimerization. An ideal solvent would dissolve the particular indole to be dimerized, but immediately precipitate the dimer hydrochloride when the solution is treated with gaseous HCl. Purification of an indole dimer hydrochloride by a recrystallization method is not feasible, because in solution the dimer hydrochloride equilibrates with its monomer and trimer, resulting in the formation of a mixture (indole monomer ⇌ indole dimer ⇌ indole trimer).

†Roman numerals refer to classes of compounds mentioned only in the text. Arabic numerals refer to individual compounds and compounds in the tables.