[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN CO.]

Aminoalkylphenothiazines

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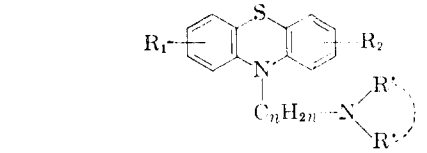
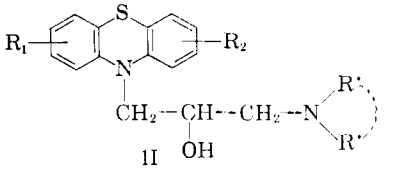
The preparation of a number of new 10-aminoalkyl- (I) and 10-aminoalkanol- (II) phenothiazines is reported. These compounds have been screened for their ability to increase the sleeping time of mice given hexobarbital, a test which has been used to select compounds for trial in mental disease. Several are highly active by this test. The sulfoxides (VII) and S,N-dioxides (VIII) of several of these compounds were prepared and found to be very active diuretics.

A considerable number of N-*t*-aminoalkylphenothiazines (I) have been tested as antihistamines, antiemetics and in mental disease.[1] The usefulness of Pyrrolazote[2] (Ia) as an antihistamine and of



Ia. R_1 and R_2 = H; $-N\begin{matrix}R'\\R''\end{matrix}$ = pyrrolidyl; C_nH_{2n} = $-(CH_2)_2-$

b. R_1 = H; R_2 = 2 Cl; R' = CH_3; C_nH_{2n} = $-(CH_2)_3$



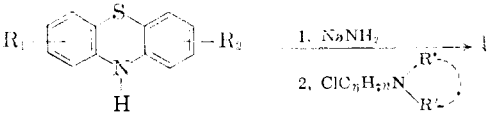
II

chloropromazine (Ib) in mental disease has encouraged the preparation of other compounds of this type and also a series with an hydroxyl group on the side chain (II).

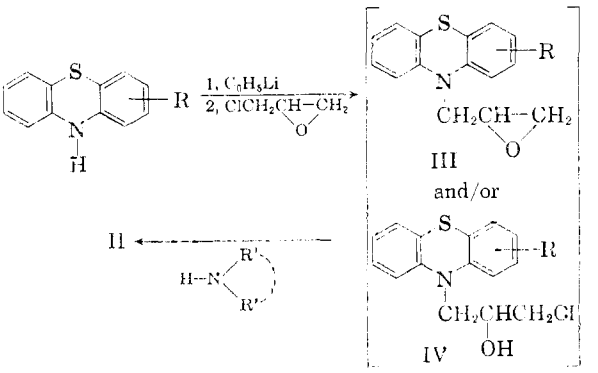
Since reserpine, chloropromazine and many other drugs used in mental disease greatly prolong the sleeping time of animals given small doses of barbiturates; this property has been used as a screening procedure. Table I lists the new phenothiazines we have made, with some of their pharmacological properties. A few previously reported compounds are included for comparison. In the course of testing these compounds for a wide variety of pharmacological activities it was found that some produced marked diuresis in rats. Although some of the compounds of types I and II showed this activity to a moderate degree, it was overshadowed by other properties. However, the sulfoxides and S,N-dioxides were much stronger diuretics. A rough measure of this activity is given in Table I and more details will be published elsewhere.[3]

Three non-amino substituted phenothiazine sulfoxides, IX, X and XI in the Experimental part, were made and found inactive as diuretics under the conditions of the test. 10-[2-(1-Pyrrolidyl)-ethyl]-phenothiazine N,S-dioxide (no. 3) has undergone extensive clinical study[4] and appears to have diuretic activity in man.

The aminoalkyl phenothiazines (I) (nos. 1–25 in the Tables) were prepared by the action of the appropriate amino alkyl chloride on the sodio derivative of the requisite phenothiazine.



The aminoalkanol phenothiazines (II) (nos. 28–36 in the Tables) were prepared by the action of epichlorohydrin on the lithium derivative of the appropriate phenothiazine followed by reaction with the requisite secondary amine.



III and/or IV

In reporting this reaction on unsubstituted phenothiazine, Charpentier[5] formulates the intermediate as the epxoide III (R = H). We have been unable to crystallize the intermediate, but infrared and chlorine analysis on the crude material (R = 2 Cl) indicate that it may be IV or a mixture of III and IV.

In an attempt to improve the process for the aminoalkanol phenothiazines (II), the lithium derivative of 2-chlorophenothiazine was treated with epoxyacrolein diethylacetal giving the hydroxyacetal V.[6] Although this could be converted to the 2,4-dinitrophenylhydrazone VI (R = 2,4-$(NO_2)_2C_6H_3NHN{=}$) or to the semicarbazone VI (R = $NH_2CONHN{=}$), all attempts failed to obtain the free hydroxy aldehyde or the amino compound II.

The sulfoxides VII were prepared by the action of hydrogen peroxide on the hydrochloride salts

(1) P. Viaud, *J. Pharm. Pharmacol.*, **6**, 361 (1954); J. P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Ruesch, S. Guldimann, V. Theus, E. Schenker and J. Renz, *Helv. Chim. Acta*, **42**, 259 (1959).

(2) The Upjohn Company brand of 10-[2-(1-pyrrolidyl)-ethyl-phenothiazine; W. B. Reid, J. B. Wright, H. G. Kolloff and J. H. Hunter, THIS JOURNAL, **70**, 3100 (1948).

(3) B. E. Graham, W. E. Brown, R. A. Zandt and W. Veldkamp, in preparation.

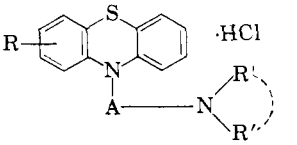
(4) R. V. Ford, D. V. Miller and M. J. Fairweather, *J. Chronic Diseases*, **8**, 694 (1958).

(5) P. Charpentier, U. S. Patent 2,595,215 (1952).

(6) This work was done in these laboratories by Dr. Burris D. Tiffany.

TABLE I

PHARMACOLOGICAL PROPERTIES

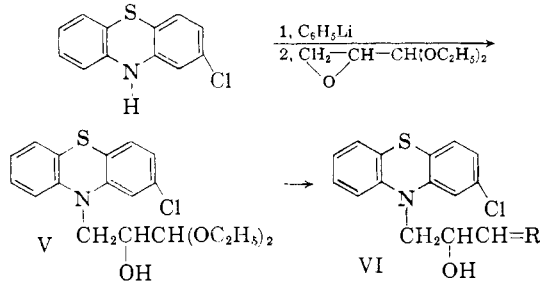


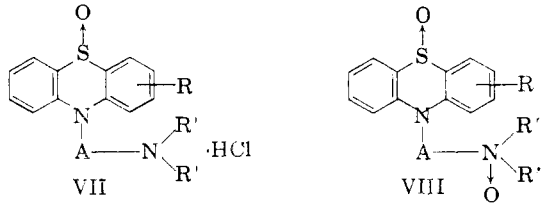
No.	Substituents on phenothiazine, R	-A-N(R')(R'')	Toxicity LD_{50}[a]	Increase in hexobarbital sleeping time,[b] %	Diuretic activity[c]
1	None	$-CH_2CH_2NCH_2CH_2CH_2CH_2$[2]	230	500	++
2	5 → O	$-CH_2CH_2N-CH_2CH_2CH_2CH_2$	230	170	++++
3	5 → O	$-CH_2CH_2N(\rightarrow O)CH_2CH_2CH_2CH_2$[d]	>1000	60	++++
4	5 di → O	$-CH_2CH_2NCH_2CH_2CH_2CH_2$	200	70	0
5	None	$-CH_2CH_2NCH(CH_3)CH_2CH_2CH_2$	650	830	---
6	5 → O	$-CH_2CH_2N(\rightarrow O)CH(CH_3)CH_2CH_2CH_2$[d]	>1000	70	+++
7	5 → O	$-CH_2CH(CH_3)N(CH_3)_2$	530	130	++++
8	5 → O	$-CH_2CH(CH_3)N(\rightarrow O)(CH_3)_2$	1000	170	++++
9	None	$-CH_2CH_2NC(CH_3)_2CH_2CH_2CH_2C(CH_3)_2$	>1000	100	0
10	None	$-CH_2CH_2N(CH_2)_3C(CH_2)_4CH_2$[e]	650	500	---
11	None	$-CH_2CH_2CH_2N(CH_3)_2$[f]	200	930	---
12	5 → O	$-CH_2CH_2CH_2N(CH_3)_2$	230	130	---
13	2Cl	$-CH_2CH_2NC(CH_3)_2CH_2CH_2CH_2C(CH_3)_2$[g]	530	260	0
14	2Cl, 5 → O	$-CH_2CH_2CH_2N(\rightarrow O)(CH_3)_2$[d]	1000	150	+++
15	2Cl	$-(CH_2)_3NCH(CH_3)CH_2CH_2CHCH_3$	530	1190	---
16	2Cl	$-(CH_2)_3NC(CH_3)_2CH_2CH_2CH_2$	170	350	0
17	2Cl	$-(CH_2)_3NC(CH_3)_2CH_2CH(CH_3)CH_2$	200	730	---
18	2Cl	$-(CH_2)_3N(CH_2)_3C(CH_2)_4CH_2$[e,h]	65	300	---
19	$2CF_3$	$-CH_2CH_2N-CH_2CH_2OCH_2CH_2$	1000	430	+
20	$2CF_3$	$-(CH_2)_3NCH(CH_3)CH_2CH_2CHCH_3$	460	290	0
21	$2CF_3$	$-(CH_2)_3NC(CH_3)_2CH_2CH_2CH_2$	200	350	---
22	$2CF_3$	$-(CH_2)_3N(CH_2)_3C(CH_2)_4CH_2$[d]	650	40	0
23	2Cl, $8CH_3$[i]	$-(CH_2)_3NC(CH_3)_2CH_2CH_2CH_2$	200	200	+++
24	$2CH_3$, $3CH_3$	$-(CH_2)_3NC(CH_3)_2CH_2CH_2CH_2$	200	130	---
25	2Cl, $7CH_3$, $8CH_3$[i]	$-(CH_2)_3NC(CH_3)_2CH_2CH_2CH_2$	200	90	++
26	3Cl	$-CH_2CH_2NCH_2CH_2CH_2CH_2$	170	730	+++
27	3Cl, 5 → O	$-CH_2CH_2N(\rightarrow O)CH_2CH_2CH_2CH_2$[d]	650	80	+
28	5 → O	$-CH_2CH(OH)CH_2N(CH_3)_2$	650	..	---
29	None	$-CH_2CH(OH)CH_2NCH_2CH_2CH_2CH_2$[j]	..	..	---
30	2Cl	$CH_2CH(OH)CH_2N(CH_3)_2$	200	670	+
31	2Cl, 5 → O	$-CH_2CH(OH)CH_2N(CH_3)_2$	300	..	++++
32	2Cl, 5 → O	$-CH_2CH(OH)CH_2N(\rightarrow O)(CH_3)_2$[d]	1000	..	++++
33	2Cl	$-CH_2CH(OH)CH_2NC(CH_3)_2CH_2CH_2CH_2$	300	890	---
34	2Cl	$-CH_2CH(OH)CH_2NCH(CH_3)(CH_2)_3CHCH_3$	1000	60[k]	0
35	$2CF_3$	$-CH_2CH(OH)CH_2N(CH_3)_2$	200	520	+++
36	$2CF_3$	$-CH_2CH(OH)CH_2NCH(CH_3)CH_2CH_2CHCH_3$	530	460	0
37	2Cl	$-(CH_2)_3N(CH_3)_2$[l]	160	1100	+++

[a] The compounds were administered to mice intraperitoneally; the values (mg./kg.) are approximations with an accuracy of about +100% to −50%. [b] The compounds were dissolved or suspended in aqueous carboxymethylcellulose in doses representing 20% of their LD_{50} values and tested for prolongation of hexobarbital sleeping time by a modification of the method of C. A. Winter [*J. Pharmacol. Exp. Therap.*, **94**, 7 (1948)]. [c] Administered orally to rats at 20 mg./kg.; diuretic activity was determined by a modification of the method of W. L. Lipschitz, Z. Hadidian and A. Kerpscar [*J. Pharmacol.*

Exp. Therap., **79**, 97 (1943)], and is calculated as percentage increase in urine volume in excess of control: 0, <21%; +, 21–35%; ++, 36–50%; +++, 51–75%; ++++, >75%. [d] Isolated and tested as the free base instead of the hydrochloride. [e] Preparation previously described [R. B. Moffett, THIS JOURNAL, **79**, 3186 (1957)]. [f] Promazine hydrochloride; P. Charpentier, U. S. Patent 2,519,886 (1950). [g] This free base was dissolved in dilute sulfuric acid for testing. [h] This free base was dissolved in dilute acetic acid for testing. [i] The positions of the substituents on the phenothiazine ring are assumed from analogous thionation reactions which give predominantly 2-isomers [S. P. Massie, *Chem. Revs.*, **54**, 797 (1954)]. [j] Isolated as the oxalate salt instead of the hydrochloride; the oxalate ion rendered it undesirable for animal testing. [k] This hydrochloride is quite insoluble in water; it was tested in suspension which may account for the low activity of this particular salt. The activity was essentially unchanged at all doses tested (down to 2.5% of its LD_{50}). [l] Chloropromazine hydrochloride (Ib) [P. Charpentier, P. Gailliot, R. Jacob, J. Gaudechon and P. Buisoon, *Compt. rend.*, **235**, 59 (1952)].

and the S,N-dioxides VIII by hydrogen peroxide on the free bases. The 3-chloro derivative of Pyrrolazote[2] (no. 26) was prepared from Pyrrolazote[2] sulfoxide (no. 2) by the action of hydrochloric acid.[7]





The chemical properties of the new aminoalkyl- and aminoalkanolphenothiazines are listed in Table II. An example of each type of reaction used in their preparation is given in the Experimental part along with several new intermediates and other related compounds.

Acknowledgments.—The authors are indebted to Dr. Patrick H. Seay, Mr. William Veldkamp, Mr. Boyd E. Graham and Associates of the Department of Pharmacology for the pharmacological results and to Dr. Richard V. Heinzelman of the Department of Chemistry for guidance.

Experimental[8]

10-[2-(1-Pyrrolidyl)-ethyl]-phenothiazine.—A mixture of 1550 g. of Pyrrolazote hydrochloride,[2] 3 l. of 7% aqueous sodium hydroxide and 2 l. of ether was shaken. On standing overnight 300 g. of the crystalline free base hydrate had separated which had the properties listed in Table II (no. 1).

10-[2-(1-Pyrrolidyl)-ethyl]-phenothiazine Sulfoxide Hydrochloride.—To a solution of 300 g. (0.9 mole) of Pyrrolazote hydrochloride[2] in 1 l. of ethanol was added 108 g. (0.945 mole) of 30% hydrogen peroxide. After standing at room temperature for 72 hours, the solution was heated under reflux with stirring for one hour. After cooling, an aqueous slurry of 0.1 g. of 30% platinum-on-charcoal was added and the mixture was vigorously stirred for 2 hours to destroy the remaining hydrogen peroxide. A test for peroxide was negative.[9] After removing the catalyst by filtration, the solvent was distilled under reduced pressure. The residue was taken up in 1 l. of isopropyl alcohol, treated with 10 g. of decolorizing charcoal (Darco G-60) at the boiling point, filtered and cooled, giving 274.4 g. (87%) of crystals with the properties given in Table II (no. 2).

Free Base.—To a solution of 75 g. (0.215 mole) of this hydrochloride in 300 ml. of water was added 75 ml. of 20% sodium hydroxide. The resulting solid was collected, dried and recrystallized twice from isopropyl alcohol giving 45 g. (67%) of crystals, m.p. 153–155°.

Anal. Calcd. for $C_{18}H_{20}N_2OS$: C, 69.20; H, 6.45; N, 8.97. Found: C, 69.20; H, 6.27; N, 8.85.

10-[2-(1-Pyrrolidyl)-ethyl]-phenothiazine N,S-Dioxide.—A mixture of 1.5 kg. (4.5 moles) of Pyrrolazote hydrochloride[2] and 200 g. (5.0 moles) of sodium hydroxide in 2 l. of water was extracted with 3 l. of benzene in two portions. The benzene was distilled under reduced pressure and the residual free base in a 12-l. flask was dissolved in 4 l. of ethanol. To this was added 1530 g. (13.5 moles) of 30% hydrogen peroxide and the solution was kept at 25–50° by slight cooling for 60 hours. An aqueous slurry of 1.0 g. of 30% platinum-on-charcoal was added and the mixture was vigorously stirred for 4 hours to destroy the excess hydrogen peroxide. A test for peroxides was negative.[9] After removing the catalyst by filtration the solvent was distilled under reduced pressure at a temperature below 50°. The residue was crystallized from 6 l. of isopropyl alcohol. The product was washed with acetone and thoroughly dried giving 1.26 kg. (85%) of white crystals with the properties listed in Table II (no. 3).

10-[2-(1-Pyrrolidyl)-ethyl]-phenothiazine S,S-Dioxide.—A solution of 15.0 g. (0.043 mole) of Pyrrolazote hydrochloride,[2] 15 ml. of 30% hydrogen peroxide and 0.5 ml. of sulfuric acid in 100 ml. of acetic acid was allowed to stand for 16 hours and then heated on a steam-bath for 1 hour. An additional 15 ml. of 30% hydrogen peroxide was added and the heating was continued for 0.5 hour more. After cooling, it was poured into a solution of 80.0 g. of sodium hydroxide in 600 ml. of water. The gummy solid was crystallized from isopropyl alcohol giving 3.1 g. (22%) of crystals with the properties given in Table II (no. 4[b]).

Hydrochloride.—A slight excess of ethanolic hydrogen chloride was added to a suspension of 8.0 g. of the above free base in 100 ml. of ethyl acetate. The solid was recrystallized from ethanol containing a little water giving crystals with the properties given in Table II (no. 4).

3-(2,2,4-Trimethyl-1-pyrrolidyl)-propanol.—A mixture of 113.2 g. (1.0 mole) of 2,2,4-trimethylpyrrolidine[10] and 94.6 g. (1.0 mole) of 3-chloropropanol in a 1-l. flask was heated under reflux with stirring. The reaction started when the temperature reached about 120°. When the reaction subsided, the solution was heated at 120–150° for 15 minutes and cooled. After thoroughly mixing with 160 ml. of 35% sodium hydroxide, the product was extracted with several portions of ether. The ether solution was dried over potassium carbonate and filtered. After removing the solvent, the residue was distilled through a short column giving 128 g. (75%) of colorless liquid, b.p. 105–108° (13 mm.), $n^{25}D$ 1.458.

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 69.95; H, 11.93; N, 8.48.

3-(2,2,4-Trimethyl-1-pyrrolidyl)-propyl Chloride Hydrochloride.—A slight excess of hydrogen chloride gas was passed into a solution of 58.4 g. (0.34 mole) of 3-(2,2,4-trimethyl-1-pyrrolidyl)-propanol with stirring and cooling in an ice-bath. Then 29 ml. (0.4 mole) of thionyl chloride was slowly added with stirring and cooling. The cooling bath was removed and the flask was heated under reflux for 1.5 hours. Hydrogen chloride and sulfur dioxide were evolved

(7) A. C. Schmalz and A. Burger, THIS JOURNAL, **76**, 5455 (1954).

(8) Melting points are uncorrected. Analyses are by Mr. William A. Struck and staff of our Analytical Chemistry Laboratory. Infrared spectra were obtained by Dr. James L. Johnson and associates of our Department of Physical and Analytical Chemistry on the final products. In all cases they were consistent with the assigned structures.

(9) J. L. O'Brien, *Chem. Eng. News*, **33**, 2008 (1955).

(10) R. B. Moffett and J. L. White, *J. Org. Chem.*, **17**, 407 (1952).

TABLE II

CHEMICAL PROPERTIES

No. Table I	Yield,[a] %	M.p., °C.	Crystn. solvent	Empirical formula	Carbon, % Calcd.	Carbon, % Found[g]	Hydrogen, % Calcd.	Hydrogen, % Found[g]	Chlorine, % Calcd.	Chlorine, % Found[g]	Nitrogen, % Calcd.	Nitrogen, % Found[g]	Sulfur, % Calcd.	Sulfur, % Found[g]
1[b]	..	68–100 d.	$Et_2O + H_2O$	$C_{18}H_{20}N_2S \cdot H_2O$[c]	68.75	68.59	7.05	6.88	...	...	8.91	8.83	...	...
2	87[d]	218–220	*i*-PrOH	$C_{18}H_{21}ClN_2OS$	61.96	62.29	6.07	6.04	10.16	10.14	8.03	7.96	9.19	9.26
3	85[d]	156–158	*i*-PrOH	$C_{18}H_{20}N_2O_2S$	65.82	65.64	6.14	6.03	...	...	8.53	8.57	9.76	9.78
3[e]	94[f]	144–155 d.	EtOH + Et_2O	$C_{18}H_{21}ClN_2O_2S$	59.24	58.99	5.80	5.90	9.72	9.60	7.68		8.79	8.60
3[g]	64[f]	127–129	EtOAc	$C_{20}H_{24}N_2O_4S$	61.83	62.19	6.23	6.32	...	...	7.21	6.99	8.26	8.42
4[b]	22[d]	167–169	*i*-PrOH	$C_{18}H_{20}N_2O_2S$	65.82	65.82	6.14	6.16	...	...	8.53	8.44	9.76	9.96
4	80[f]	273–275	EtOH + H_2O	$C_{18}H_{21}ClN_2O_2S$	59.24	58.96	5.80	5.78	9.72	9.81	7.68	7.70	...	...
5	35[h]	194–195.5	EtOH + Et_2O	$C_{19}H_{23}ClN_2S$	65.78	65.69	6.68	6.95	10.22	10.21	8.08	8.52	9.24	9.20
6	39[i]	123.5–125.5	*i*-PrOH + Et_2O	$C_{19}H_{21}N_2O_2S$	66.73	66.32	6.46	6.42	...	...	8.16	8.27	9.34	9.15
7	43[j]	253–255 d.	EtOH + Et_2O	$C_{17}H_{21}ClN_2OS$	60.61	60.33	6.28	6.38	10.53	10.84	8.32	8.87	9.52	9.56
8	31[j]	187–191	*i*-PrOH	$C_{17}H_{21}ClN_2O_2S$	57.86	58.01	6.00	6.18	10.05	9.51	7.94	8.29	9.09	9.01
9	55[k]	230–232	EtOH	$C_{23}H_{31}ClN_2S$	68.54	68.85	7.75	8.07	8.80	8.73	..	..	...	...
11[l]	74	173–175	EtOH + MeOH	$C_{19}H_{22}N_2O_5S$	60.94	61.11	5.92	5.97	...	...	7.48	7.73	8.56	8.36
12	81[m]	198–200	EtOH + EtOAc	$C_{17}H_{21}ClN_2OS$	60.61	60.75	6.28	6.24	10.53	10.24	8.32	8.24	...	...
12[n]	75	200–202	MeOH	$C_{19}H_{22}N_2O_5S$	58.44	58.24	5.68	5.69	...	...	7.18	7.16	8.21	8.42
12[o]	67	114–116	Et_2O	$C_{17}H_{20}N_2OS$	67.96	68.29	6.71	6.78	...	...	9.33	9.39	10.67	10.81
13	20[p]	129.5–131.5	EtOAc	$C_{23}H_{29}ClN_2S$	68.89	68.88	7.29	7.06	8.84	8.78	..	..	...	...
14	54[q]	141–142	$CHCl_3$ + acetone	$C_{17}H_{18}ClN_2O_2S \cdot {}^1/_2H_2O$	...	...	..	..	9.85	10.17	7.79	7.28	8.91	8.76
15[r]	60	172–175	MeOH + EtOH	$C_{23}H_{27}ClN_2O_4S$	59.66	59.65	5.88	6.08	...	...	6.05	6.05	6.92	6.36
15	20[s]	228–230	*i*-PrOH	$C_{21}H_{26}Cl_2N_2S$	61.60	61.22	6.40	6.66	17.32	17.09	6.84	6.86	...	...
16	87	215–217	EtOH	$C_{21}H_{26}Cl_2N_2S$	61.60	61.45	6.40	6.35	17.32	16.95	6.84	6.65	7.83	7.93
17[b]	..	56–58	EtOH	$C_{22}H_{27}ClN_2S$	68.28	68.08	7.03	7.42	9.16	9.03	..	..	...	...
17	72	177–179	EtOH + MeCOEt	$C_{22}H_{28}Cl_2N_2S$	62.40	62.17	6.66	6.37	16.75	16.45	6.62	6.55	7.57	8.06
19[b]	34	107–109	EtOAc	$C_{19}H_{19}F_3N_2OS$	59.98	59.65	5.03	5.08	...	...	7.37	7.45	8.43	8.37
19	79[f]	205–208	EtOH + EtOAc	$C_{19}H_{20}ClF_3N_2OS$	54.74	54.94	4.84	4.88	...	...	6.72	6.61	7.69	7.62
20	84[t]	218–220	EtOH + EtOAc	$C_{22}H_{26}ClF_3N_2S$	59.65	59.77	5.92	5.51	...	...	6.33	6.52	7.24	7.32
21	47[u]	170–172	EtOH + EtOAc	$C_{22}H_{26}ClF_3N_2S$	59.65	59.58	5.92	5.97	...	...	6.33	6.37	7.24	7.26
22	32	82–84	EtOAc	$C_{25}H_{29}F_3N_2S$	67.24	67.30	6.55	7.06	...	...	6.27	6.37	7.18	7.01
23	49[v]	183–186	EtOH + EtOAc	$C_{22}H_{28}Cl_2N_2S$	62.16	62.22	6.66	6.25	16.65	16.67	..	..	7.57	7.74
24	39[w]	165–168	EtOH + EtOAc	$C_{23}H_{31}ClN_2S$	68.54	68.56	7.75	7.88	8.80	8.92	6.95	6.90	...	...
25	51[x]	182–184	EtOH + EtOAc	$C_{23}H_{30}Cl_2N_2S$	63.14	63.32	6.91	7.49	16.21	16.09	6.41	6.76	7.33	7.34
26	41	170–173	$C_8H_5CH_3$	$C_{18}H_{20}Cl_2N_2S$	58.85	58.96	5.49	5.16	19.30	18.62	7.63	7.62	...	...
27	21	133.5–135	*i*-PrOH	$C_{18}H_{19}ClN_2O_2S \cdot H_2O$[y]	56.76	56.50	5.56	5.54	9.31	9.16	7.36	7.99	8.42	8.80
28	57[z]	122–124	*i*-PrOH	$C_{17}H_{21}ClN_2O_2S$	57.06	57.20	6.00	6.56	10.05	9.76	7.94	7.45	9.09	9.36
29	29	194–196	EtOH + H_2O	$C_{21}H_{24}N_2O_5S$	60.56	60.53	5.81	5.45	...	...	6.73	6.62	7.70	7.79
30[b]	..	98–100	EtOH + H_2O	$C_{17}H_{19}ClN_2OS$	...	...	..	..	10.59	10.53	..	..	...	...
30	54	176–178	MeOH + acetone	$C_{17}H_{20}Cl_2N_2OS$	54.98	54.64	5.43	5.73	19.10	18.92	7.55	7.59	...	...
31	59[aa]	215–217	*i*-PrOH + H_2O + acetone	$C_{17}H_{20}Cl_2N_2O_2S$	52.71	52.97	5.20	5.07	18.31	18.44	7.23	6.97	8.28	8.17
32	63[aa]	163–164	*i*-PrOH + acetone	$C_{17}H_{19}ClN_2O_3S$[bb]	55.65	53.51	5.22	5.41	9.66	9.63	7.64	7.62	8.74	8.38
33	19	186–188	MeOH + EtOAc	$C_{21}H_{26}Cl_2N_2OS$	59.29	59.07	6.16	6.18	16.67	16.46	6.59	6.45	...	...

TABLE II (*Continued*)

No. Table I	Yield,[a] %	M.p., °C.	Crystn. solvent	Empirical formula	Carbon, % Calcd.	Carbon, % Found[g]	Hydrogen, % Calcd.	Hydrogen, % Found[g]	Chlorine, % Calcd.	Chlorine, % Found[g]	Nitrogen, % Calcd.	Nitrogen, % Found[g]	Sulfur, % Calcd.	Sulfur, % Found[g]
34	12	287–289	MeOH + EtOAc	$C_{22}H_{28}Cl_2N_2OS$	60.13	60.03	6.42	6.38	16.14	15.97	6.38	6.24	7.30	7.3
35	17	146–149	EtOAc	$C_{18}H_{20}ClF_3N_2OS$	53.39	53.45	4.98	4.77	...	...	6.92	6.88	7.92	7.3
36	29	256–258	MeOH + EtOAc	$C_{22}H_{25}ClF_3N_2OS$	57.57	57.72	5.71	5.88	...	...	6.10	6.08	6.99	7.3

[a] Unless otherwise indicated this is the over-all yield from the corresponding phenothiazine unsubstituted in the 10- position. [b] This is the free base corresponding to the hydrochloride of Table I. [c] Calculated for one H_2O: 5.73. Found (by Karl Fischer method): 5.76. [d] This yield based on 10-[2-(1-pyrrolidyl)-ethyl]-phenothiazine hydrochloride. [e] This is the hydrochloride salt of the free base of Table I. [f] Yield of salt from corresponding free base. [g] This is the acetate salt of the free base of Table I. [h] The free base was distilled, b.p. 193° (0.07 mm.), giving a 35% yield of viscous oil which was converted to the hydrochloride in nearly quantitative yield. [i] Yield based on above hydrochloride (no. 5). [j] Yield based on 10-(2-dimethylaminopropyl)-phenothiazine (promethazine) hydrochloride. [k] This hydrochloride separated on the addition of aqueous hydrochloric acid to the toluene solution of the reaction product; the free base was not distilled. [l] This is promazine oxalate salt corresponding to the hydrochloride of Table I. It was prepared *via* the corresponding free base [P. Charpentier, U. S. Patent 2,519,886 (1950)] in a 74% over-all yield from phenothiazine. [m] This yield is based on 10-(3-dimethylaminopropyl)-phenothiazine (promazine) hydrochloride. [n] This is the oxalate salt; it was prepared from promazine oxalate (no. 11[e]) by the action of hydrogen peroxide. [o] This is the free base, promazine sulfoxide; it was prepared from the oxalate (no. 12[e]). [p] This free base was not distilled but crystallized from ethyl acetate with the use of decolorizing charcoal. [q] This yield is based on 2-chloro-10-(3-dimethylaminopropyl)-phenothiazine (chloropromazine) (Table I, footnote *k*); the product crystallized from a chloroform solution on the addition of acetone. The infrared spectrum indicates it is a hydrate. Calcd. for $C_{17}H_{19}ClN_2O_2S/_2H_2O$: O, 11.28. Found: O, 11.12. [r] This is the oxalate salt corresponding to the hydrochloride of Table I. The free base was not distilled but converted to this oxalate in ether. It was recrystallized from ethanol + methanol, reconverted to the non-crystalline free base from which the hydrochloride was prepared in the usual way. [s] This yield is based on the above oxalate; the hydrochloride crystallized with difficulty. [t] The free base was distilled, b.p. 182° (0.15 mm.), giving an 84% yield of viscous oil; it was converted to the hydrochloride in nearly quantitative yield. [u] This is the yield of the distilled free base, b.p. 180–190° (0.6 mm.); it was converted to the hydrochloride with the properties listed. [v] The free base was prepared from 2-chloro-8- methylphenothiazine [P. Charpentier, U. S. Patent 2,645,640 (1953)] and distilled, b.p. 196–200° (0.05 mm.), giving a 78% yield of viscous oil; it was converted to the hydrochloride in 63% yield. [w] The free base was distilled, b.p. 200–202° (0.06 mm.), giving a 48% yield of viscous oil; it was converted to the hydrochloride in 81% yield. [x] The free base was not distilled but was converted to the hydrochloride. [y] The infrared spectrum and analysis indicate this is a hydrate. [z] This yield is based on 10-(3-dimethylamino-2-hydroxypropyl)-phenothiazine hydrochloride.[5] [aa] This yield is based on 2-chloro-10-(3-dimethylamino-2-hydroxypropyl)-phenothiazine hydrochloride (No. 30). [bb] The infrared spectrum indicates this compound may contain some water of hydration.

and the product separated. The crystals were collected, washed with benzene and ether and dried giving 69 g. (89%) of material, m.p. 162–164°.

Anal. Calcd. for $C_{10}H_{21}Cl_2N$: C, 53.10; H, 9.36; Cl, 31.35; N, 6.19. Found: C, 53.17; H, 9.00; Cl, 31.29. N, 5.86.

2-Chloro-10-[3-(2,2,4-trimethyl-1-pyrrolidyl)-propyl]-phenothiazine.—A solution of 3-(2,2,4-trimethyl-1-pyrrolidyl)-propyl chloride was prepared by shaking 39.0 g. (0.17 mole) of the corresponding hydrochloride with 50 ml. of 30% sodium hydroxide and extracting with 150 ml. of toluene in two portions. The toluene extracts were thoroughly dried over potassium carbonate and filtered.

To a suspension of 6.63 g. (0.17 mole) of sodium amide in 150 ml. of dry toluene was added 35.1 g. (0.15 mole) of 2-chlorophenothiazine[11] and the mixture was heated under reflux with stirring for 3 hours. To this was slowly added the above toluene solution of the chloride and the refluxing was continued for 6 hours. After cooling, the mixture was washed with water and extracted with 200 ml. of 1.5 *N* hydrochloric acid in two portions. The aqueous acid solutions were washed with ether and made basic with sodium hydroxide. The oily free base was extracted with 300 ml. of ether in three portions and dried over sodium sulfate. After filtration and removal of the ether, the free base was distilled giving 47 g. (81%) of viscous oil, b.p. 200° (0.15 mm.), A small sample solidified on long standing and was recrystallized from ethanol, m.p. 56–58° (Table II, no. 17[b]).

Hydrochloride.—To a solution of 47.0 g. (0.12 mole) of the above free base in 150 ml. of absolute ether, a slight excess of a solution of hydrogen chloride in absolute ether was slowly added with stirring and cooling. The hydrochloride separated as a nearly white solid and was recrystallized from 200 ml. of methyl ethyl ketone containing a little ethanol. A yield of 45.5 g. (89%) of white crystals was obtained having the properties listed in Table II (no. 17).

Ethyl 1-Oxalyl-2,2,6,6-tetramethylpiperidine.—To a solution of 66.5 g. (0.47 mole) of 2,2,6,6-tetramethylpiperidine[12] in 100 ml. of benzene was slowly added with stirring under nitrogen 88.0 g. (0.64 mole) of ethyl oxalyl chloride. The mixture was heated under reflux for 1 hour, 74.0 g. of N-ethylpiperidine in 100 ml. of benzene was added and the heating was continued for 5 hours more. Ice and dilute hydrochloric acid were added and the mixture was extracted well with ether. The ether solutions were washed with water, dilute sodium hydroxide and again with water and finally with saturated sodium chloride solution. After removing the solvent, the product was distilled through a short column giving 104.5 g. (92.4%) of colorless liquid, b.p. 85° (0.02 mm.), $n^{25}D$ 1.4770.

Anal. Calcd. for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.60; N, 5.80. Found: C, 64.88; H, 9.41; N, 5.70.

2-(2,2,6,6-Tetramethyl-1-piperidyl)-ethanol.—To a suspension of 7.6 g. (0.2 mole) of lithium aluminum hydride in 50 ml. of dry tetrahydrofuran was added, dropwise with vigorous stirring under nitrogen, a solution of 14.48 g. (0.06 mole) of ethyl 1-oxalyl-2,2,6,6-tetramethylpiperidine in 25 ml. of tetrahydrofuran. The mixture was then heated under reflux with stirring for 4.5 hours. The excess lithium aluminum hydride was decomposed by the very slow addition of ethyl acetate in ether. A gel separated and the mixture was poured onto ice and acidified with hydrochloric acid. The solution was extracted twice with ether and made very strongly basic with sodium hydroxide. This was continuously extracted with ether (with stirring) for 11.5 hours. These extracts were dried over potassium carbonate, filtered and the ether was distilled. The residue crystallized and was recrystallized from hexane, giving 9.82 g. (88.5%) of white crystals, m.p. 96–98°.

Anal. Calcd. for $C_{11}H_{23}NO$: C, 71.30; H, 12.51; N, 7.56. Found: C, 71.66; H, 12.64; N, 7.21.

2-(2,2,6,6-Tetramethyl-1-piperidyl)-ethyl Chloride Hydrochloride.—Hydrogen chloride gas was passed into a solution of 7.75 g. (0.042 mole) of 2-(2,2,6,6-tetramethyl-1-piperidyl)-ethanol in 50 ml. of benzene while cooling by an ice-bath. The hydrochloride separated as a white solid but was not isolated. Then 3.7 ml. (0.05 mole) of thionyl chloride was added with stirring and cooling. The solid dis-

(11) British Patent 716,207 (1954).

(12) N. J. Leonard and E. W. Nommensen, THIS JOURNAL, **71**, 2808 (1949).

solved and two liquid layers were formed. The ice-bath was removed and the mixture was heated under reflux with stirring for 2 hours. The mixture became homogeneous and then crystals separated. After cooling, the crystals were collected, washed with benzene and ether and dried giving 9.62 g. (95.4%) of product, m.p. 217–219°. A small sample was recrystallized from isopropyl alcohol giving colorless crystals, m.p. 219–220°.

Anal. Calcd. for $C_{11}H_{23}Cl_2N$: C, 55.00; H, 9.65; Cl, 29.52; N, 5.83. Found: C, 55.16; H, 9.38; Cl, 29.37; N, 6.07.

3-(2,5-Dimethyl-1-pyrrolidyl)-propanol was prepared as described above for the 2,2,4-trimethyl analog from 94.6 g. (1.0 mole) of 3-chloropropanol and 99.2 g. (1.0 mole) of 2,5-dimethylpyrrolidine, giving 106.9 g. (68%) of colorless liquid, b.p. 106° (13 mm.), $n^{25}D$ 1.4632.

Anal. Calcd. for $C_9H_{19}NO$: C, 68.74; H, 12.18; N, 8.91. Found: C, 68.58; H, 12.16; N, 9.12.

3-(2,5-Dimethyl-1-pyrrolidyl)-pyropyl chloride hydrochloride was prepared as described above for the 2,2,4-trimethyl analog from 104 g. (0.66 mole) of 3-(2,5-dimethyl-1-pyrrolidyl)-propanol and 58 ml. (0.8 mole) of thionyl chloride, giving 83.6 g. (60%) of crystals, m.p. 137–140°.

Anal. Calcd. for $C_9H_{19}Cl_2N$: C, 50.95; H, 9.03; Cl, 33.42; N, 6.60. Found: C, 51.25; H, 9.15; Cl, 33.13; N, 6.66.

3-(2,2-Dimethyl-1-pyrrolidyl)-propanol was prepared as described above for the 2,2,4-trimethyl analog from 195.8 g. (1.97 moles) of 2,2-dimethylpyrrolidine[10] and 186.2 g. (1.97 moles) of 3-chloropropanol giving 204.5 g. (66%) of colorless liquid, b.p. 111° (17 mm.), $n^{25}D$ 1.4645.

Anal. Calcd. for $C_9H_{19}NO$: N, 8.91. Found: N, 8.93.

3-(2,2-Dimethyl-1-pyrrolidyl)-propyl chloride hydrochloride was prepared as described above for the 2,2,4-trimethyl analog from 46.3 g. (0.295 mole) of 3-(2,2-dimethyl-2-pyrrolidyl)-propanol giving 57 g. (91.5%) of crystals, m.p. 165–166°.

Anal. Calcd. for $C_9H_{19}Cl_2N$: C, 50.95; H, 9.03; Cl, 33.42; N, 6.60. Found: C, 50.70; H, 8.89; Cl, 33.40; N, 6.59.

1-(γ-Hydroxypropyl-1-azaspiro[4.5]decane hydrochloride was prepared from the free base (Table I, footnote *e*) and recrystallized from ethanol; m.p. 182–184°.

Anal. Calcd. for $C_{12}H_{24}ClNO$: C, 61.65; H, 10.35; Cl, 15.17; N, 5.99. Found: C, 61.79; H, 10.38; Cl, 15.17; N, 6.17.

4-Chloro-N-(3,4-xylyl)-anthranilic Acid.—A solution of 106.0 g. (0.55 mole) of 2,4-dichlorobenzoic acid and 36.4 g. (0.55 mole) of 85% potassium hydroxide in 400 ml. of *n*-amyl alcohol was heated to 133° and 14 ml. of water was removed. Then 4.0 g. of copper powder and 145.4 g. (1.2 moles) of 3,4-dimethylaniline were added and the mixture was heated under reflux with stirring for 5 hours. A solution of 29.2 g. (0.275 mole) of sodium carbonate in 150 ml. of water was added and the amyl alcohol and excess 3,4-dimethylaniline were removed by steam distillation. After filtration, the solution was acidified with hydrochloric acid. The solid acid was recrystallized from benzene giving 103 g. (68%) of yellow-greenish crystals, m.p. 208–210°.

Anal. Calcd. for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; Cl, 12.86; N, 5.08. Found: C, 65.22; H, 4.99; Cl, 13.18; N, 5.20.

3'-Chloro-3,4-dimethyldiphenylamine.—The above acid (97 g., 0.35 mole) was heated in an oil-bath under an air-cooled reflux condenser to a bath temperature of 280° for 2 hours. The residue was dissolved in 250 ml. of benzene, decolorized by filtration through Magnesol, and cooled in the refrigerator giving 68.5 g. (84%) of white crystals, m.p. 35–37°. Recrystallization from pentane raised the melting point to 54–55°.

Anal. Calcd. for $C_{14}H_{14}ClN$: C, 72.56; H, 6.09; Cl, 15.30; N, 6.05. Found: C, 72.23; H, 5.82; Cl, 15.39; N, 6.21.

2-Chloro-7,8-dimethylphenothiazine.—A mixture of 64.7 g. (0.278 mole) of 3'-chloro-3,4-dimethyldiphenylamine, 17.8 g. (0.556 mole) of sullfur and 1.0 g. of iodine was heated under an air-cooled reflux condenser to about 140° for 1 hour. The product was dissolved in hot chlorobenzene, filtered through Magnesol and cooled giving 30.6 g. (42%) of greenish crystals, m.p. 252–253° (Table I, footnote *i*).

Anal. Calcd. for $C_{14}H_{12}ClNS$: C, 64.23; H, 4.62; Cl, 13.55; N, 5.35; S, 12.25. Found: C, 64.12; H, 4.36; Cl, 13.46; N, 5.39; S, 12.16.

3,4-Dimethyldiphenylamine was prepared as described above for 3'-chloro-3,4-dimethyldiphenylamine from 93 g. (0.385 mole) of N-(3,4-xylyl)-anthranilic acid.[13] The product was distilled, b.p. 113° (0.05 mm.), and recrystallized from pentane giving 59 g. (78%) of nearly white solid, m.p. 56–57°.

Anal. Calcd. for $C_{14}H_{15}N$: C, 85.23; H, 7.66; N, 7.10. Found: C, 85.16; H, 7.65; N, 7.35.

2,3-Dimethylphenothiazine.—A mixture of 54.0 g. (0.275 mole) of 3,4-dimethyldiphenylamine, 17.6 g. (0.55 mole) of sulfur and 1.0 g. of iodine was heated under an air-cooled reflux condenser to about 140° for 1 hour. The product was recrystallized several times from benzene giving 25 g. (40%) of greenish-yellow crystals, m.p. 202–205°.

Anal. Calcd. for $C_{14}H_{13}NS$: C, 73.97; H, 5.76; N, 6.16; S, 14.10. Found: C, 74.25; H, 5.98; N, 6.18; S, 14.19.

4-Chloro-N-(*m*-tolyl)-anthranilic acid was prepared as described above for 4-chloro-N-(3,4-xylyl)-anthranilic acid from 106 g. (0.55 mole) of 2,4-dichlorobenzoic acid and 160 g. (1.5 moles) of *m*-toluidine. The product was recrystallized from benzene giving 78 g. (54%) of solid, m.p. 193–196°. Recrystallization raised the melting point to 198–200°.

Anal. Calcd. for $C_{14}H_{12}ClNO_2$: C, 64.25; H, 4.62; Cl, 13.55; N, 5.35. Found: C, 64.12; H, 4.61; Cl, 13.64; N, 5.30.

3-Chloro-3'-methyldiphenylamine was prepared as described above for 3'-chloro-3,4-dimethyldiphenylamine from 68 g. (0.26 mole) of the above acid. The product was twice distilled giving 56.3 g. (95%) of liquid, b.p. 114–116° (0.1 mm.), $n^{25}D$ 1.6352.

Anal. Calcd. for $C_{13}H_{12}ClN$: C, 71.71; H, 5.56; Cl, 16.29; N, 6.44. Found: C, 71.28; H, 5.63; Cl, 16.33; N, 6.46.

N-(3-Trifluoromethylphenyl)-anthranilic acid was prepared as described above for 4-chloro-N-(3,4-xylyl)-anthranilic acid, from 95.5 g. (0.61 mole) of *o*-chlorobenzoic acid, 40.3 g. (0.61 mole) of 85% potassium hydroxide, 300 ml. of *n*-amyl alcohol, 196 g. (1.22 moles) of 3-trifluoromethylaniline and 5.0 g. of copper powder. The product was recrystallized twice from cyclohexane giving 107.2 g. (62%) of crystals, m.p. 134–136°.

Anal. Calcd. for $C_{14}H_{10}F_3NO_2$: C, 59.79; H, 3.58; N, 4.98. Found: C, 59.68; H, 3.39; N, 4.81.

N-(2,3-Dichlorophenyl)-anthranilic acid was prepared as described above for 4-chloro-N-(3,4-xylyl)-anthranilic acid, from 120.6 g. (0.73 mole) of *o*-chlorobenzoic acid and 250 g. (1.54 moles) of 2,3-dichloroaniline. The yield was 185 g. (85%) of crystals, m.p. 256–257°.

Anal. Calcd. for $C_{13}H_9Cl_2NO_2$: C, 55.34; H, 3.23; Cl, 25.13; N, 4.97. Found: C, 55.04; H, 3.35; Cl, 25.03; N, 5.20.

2,3-Dichlorodiphenylamine was prepared as described above for 3'-chloro-3,4-dimethyldiphenylamine, using 175 g. (0.62 mole) of the above acid. The product was distilled, b.p. 112° (0.025 mm.), giving 88 g. (60%) of liquid, $n^{25}D$ 1.6493.

Anal. Calcd. for $C_{12}H_9Cl_2N$: C, 60.53; H, 3.81; Cl, 29.78. Found: C, 60.95; H, 3.89; Cl, 29.51.

4-Chloro-N-(3-trifluoromethylphenyl)-anthranilic acid was prepared as described for 4-chloro-N-(3,4-xylyl)-anthranilic acid, using 95.5 g. (0.5 mole) of 2,4-dichlorobenzoic acid and 241.7 g. (1.5 moles) of *m*-trifluoromethylaniline. The product was recrystallized from benzene giving 75 g. (48%) of crystals, m.p. 205–208°.

Anal. Calcd. for $C_{14}H_9ClF_3NO_2$: C, 53.26; H, 2.87; N, 4.44. Found: C, 53.10; H, 2.49; N, 4.45.

3-Chloro-3'-methoxydiphenylamine was prepared as described above for 3'-chloro-3,4-dimethyldiphenylamine, using 45.0 g. (0.16 mole) of 4-chloro-N-(3-methoxyphenyl)-

(13) P. Kranzlein, *Ber.*, **70B**, 1776 (1937).

anthranilic acid.[14] The product was distilled giving 31.5 g. (84%) of liquid, b.p. 133–136° (0.05 mm.), $n^{25}D$ 1.6408.

Anal. Calcd. for $C_{13}H_{12}ClNO$: C, 66.81; H, 5.18; Cl, 15.17; N, 5.99. Found: C, 66.65; H, 5.07; Cl, 15.20; N, 5.79.

3-Chloro-10-[2-(1-pyrrolidyl)-ethyl]-phenothiazine.—A solution of 39.0 g. (0.122 mole) of 10-[2-(1-pyrrolidyl)-ethyl]-phenothiazine sulfoxide in 150 ml. of 6 *N* hydrochloric acid was stirred at room temperature for 2 hours and then on a steam-bath for 3 hours. After standing overnight, the dark green solution was poured into 300 ml. of ice-water, made basic with sodium hydroxide, and extracted with ether. After washing with water and drying over sodium sulfate, the solution was filtered, the solvent was removed and the residue distilled. A yield of 28 g. (68%) of oily free base was obtained, b.p. 186–191° (0.05 mm.).

Hydrochloride.—A slight excess of ethanolic hydrogen chloride was added to an ethereal solution of the free base precipitating the hydrochloride. This was recrystallized three times from a mixture of ethanol and ethyl acetate giving crystals with the properties given in Table II (no. 26).

2-Chloro-10-(3-dimethylamino-2-hydroxypropyl)-phenothiazine Hydrochloride.—Phenyllithium[15] was prepared in a 2-l. flask (fitted with a stirrer, thermometer, reflux condenser, dropping funnel and inlet for nitrogen) from 7.0 g. (1.0 mole) of lithium and 80.0 g. (0.5 mole) of bromobenzene in 500 ml. of absolute ether. The flask was cooled by an ice–salt mixture to 0° and 70 g. (0.3 mole) of 2-chlorophenothiazine[11] was added in small portions keeping the temperature at 0° (±2°). After stirring under nitrogen at 0 to 2° for 15 minutes, 49 g. (0.5 mole) of epichlorohydrin in 100 ml. of absolute ether was added dropwise during 2 hours at 0° with stirring under nitrogen. The temperature was then allowed to rise to 15° during 1 hour. Then 200 ml. of water was cautiously added and after thorough stirring the mixture was filtered and the solid was extracted with ether and discarded. The filtrate was separated and the aqueous layer was extracted with ether. The ether solutions were combined and dried over sodium sulfate. After filtration, the ether was distilled under reduced pressure from a water-bath below 60°, giving a viscous brown oil which was not obtained crystalline.

This crude intermediate was dissolved in 150 ml. of benzene, cooled in an ice-bath and 50 g. (1.1 moles) of dimethylamine was added. This solution was heated with stirring in a stainless steel autoclave at 120° for 12 hours. After cooling, the solution was filtered from crystals of dimethylamine hydrochloride and the autoclave and crystals were washed with more benzene. On shaking the filtrate with dilute hydrochloric acid an oily hydrochloride separated, insoluble in both layers. The benzene layer was extracted with water. The combined aqueous layers and oily hydrochloride were washed twice with ether and made basic with dilute sodium hydroxide. The free base was extracted with several portions of ether and the ether solution was dried over sodium sulfate. After filtration the solvent was distilled under reduced pressure below 60° giving the free base as a gum which could be crystallized only with difficulty (see below).

The crude free base was dissolved in 600 ml. of acetone and a slight excess of methanolic hydrogen chloride was added. About 20 ml. of the solvent was distilled and replaced by acetone. On cooling and scratching, the hydrochloride crystallized giving 67 g. (60%) of product, m.p. 160–175°. This was dissolved in hot methanol, treated with decolorizing charcoal, filtered, diluted with acetone and cooled giving 60 g. (54%) of white crystals with the properties given in Table II (no. 30).

Free Base.—An aqueous solution of 0.3 g. of the hydrochloride was made basic with sodium carbonate. The gummy free base crystallized slowly from aqueous ethanol giving 0.22 g. of white crystals, m.p. 98–100° (Table II, no. 30 *b*).

Oxalate.—To a solution of 0.3 g. (0.0008 mole) of the above hydrochloride in 2 ml. of water was added a solution of 0.067 g. (0.0005 mole) of sodium oxalate and 0.063 g. (0.0005 mole) of oxalic acid dihydrate in 3 ml. of water. On standing in the refrigerator, 0.28 g. of white solid oxalate salt separated, m.p. 164–166°.

Anal. Calcd. for $C_{19}H_{21}ClN_2O_5S$: Cl, 8.34. Found: Cl, 8.26.

2-Chloro-10-(3,3-diethoxy-2-hydroxypropyl)-phenothiazine[6] (V).—A solution of 0.25 mole of crude 2-chlorophenothiazine N-lithium salt in 300 ml. of ether (prepared as above) was cooled to −4° and a solution of 7.3 g. (0.050 mole) of glycidaldehyde diethylacetal[16] in 20 ml. of anhydrous ether was added dropwise with stirring during about 15 minutes while the temperature rose to 3°. After 1 hour, 100 ml. of water was added dropwise with continued stirring. The layers were separated and the organic layer washed with 50 ml. of saturated sodium chloride solution. The ether solution was dried over sodium sulfate and concentrated to give 106 g. of dark oil. When this partially crystallized upon standing, it was gradually diluted with 100 ml. of methylcyclohexane and the crystals collected. Upon concentrating and much scratching the filtrate slowly yielded 13.1 g. of light brown crystals, m.p. 91–95°. The first crystals above were dissolved in methylcyclohexane, passed through a thick pad of Magnesol to partially decolorize, and concentrated. It slowly yielded fractions of nearly white crystals, m.p. 91–95°, which amounted to 34.6 g. for a total of 47.7 g. (50%) of crystals melting at 91–95°.

Anal. Calcd. for $C_{19}H_{22}ClNO_3S$: C, 60.06; H, 5.84; Cl, 9.33; N, 3.69; S, 8.44. Found: C, 60.41; H, 5.49; Cl, 9.11; N, 3.80; S, 8.45.

3-(N-2-Chlorophenothiazinyl)-lactaldehyde 2,4-Dinitrophenylhydrazone[6] (VI, R = 2,4-$(NO_2)_2C_6H_3NHN$=).—To a warm solution of 0.19 g. (0.0005 mole) of the above acetal and 0.1 g. (0.0005 mole) of 2,4-dinitrophenylhydrazine in 5 ml. of ethanol was added 3 drops of concentrated hydrochloric acid. Heating for 30 minutes and cooling yielded 0.19 g. of orange platelets, m.p. 215–216° dec. Two recrystallizations from a mixture of dimethylformamide and ethanol raised the m.p. to 221–222° dec.

Anal. Calcd. for $C_{21}H_{16}ClN_5O_5S$: C, 51.91; H, 3.32; Cl, 7.30; N, 14.42; S, 6.60. Found: C, 52.37; H, 3.61; Cl, 7.21; N, 14.21; S, 6.68.

3-(N-2-Chlorophenothiazinyl)-lactaldehyde Semicarbazone[6] (VI, R = NH_2CONHN=).—A solution of 0.76 g. (0.002 mole) of 2-chloro-N-(3,3-diethoxy-2-hydroxypropyl)-phenothiazine in 10 ml. of tetrahydrofuran was treated with 0.3 ml. of 6 *N* hydrochloric acid and boiled for 20 minutes. The resulting orange sirup was dissolved in 15 ml. of ethanol and then 0.22 g. (0.002 mole) of semicarbazide hydrochloride, 0.40 g. (0.005 mole) of sodium acetate and 2 ml. of water were added and the mixture boiled again for 30 minutes. Ethanol was added to dispel cloudiness and the solution was passed through Magnesol. The first small crop of crystals, m.p. 257° dec., was discarded. The second crop gave 0.15 g. of white crystals, m.p. 215° dec. Two recrystallizations from a mixture of dimethylformamide and water raised the m.p. to 217° dec.

Anal. Calcd. for $C_{16}H_{15}ClN_4O_2S$: C, 52.96; H, 4.17; N, 15.44; S, 8.84. Found: C, 53.05; H, 4.40; N, 15.24; S, 9.29.

10-[3-(1-Pyrrolidyl)-2-hydroxypropyl]-phenothiazine oxalate was prepared by the above method from 150 g. of crude 10-(2,3-epoxypropyl)-phenothiazine and 100 g. of pyrrolidine. Neither the free base nor the hydrochloride was obtained crystalline. The free base was converted to the oxalate salt in ether and recrystallized from isopropyl alcohol and then from 80% ethanol giving 61 g. of material with the properties listed in Table II (no. 29).

10-Cyanoethylphenothiazine Sulfoxide (IX).—A mixture of 10.0 g. (0.04 mole) of 10-cyanoethylphenothiazine,[17] 10 ml. of 30% hydrogen peroxide and 150 ml. of ethanol was allowed to stand overnight and then heated on a steam-bath with stirring for 2.5 hours. The solid gradually dissolved and on cooling the product crystallized. It was recrystallized from 95% ethanol giving 7 g. (65%) of the sulfoxide, m.p. 170–172°.

Anal. Calcd. for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44; S, 11.95. Found: C, 67.56; H, 4.50; N, 10.57; S, 12.08.

10-Carboxyethylphenothiazine Sulfoxide (X).—In a similar way this was prepared from 10.0 g. (0.04 mole) of 10-carboxyethylphenothiazine.[17] It crystallized from the reaction mixture on cooling, giving 9.5 g. (83%) of white solid, m.p. 231–233°.

(14) A. F. Bekhli, *Sbornik Statei Obshchei Khim.*, **2**, 1130 (1953); *C. A.*, **49**, 5480 (1955).

(15) L. A. Walter, *Org. Syntheses*, **23**, 83 (1943).

(16) D. I. Weisblat, B. J. Magerlein, D. R. Myers, A. R. Hanze, E. I. Fairburn and S. T. Rolfson, THIS JOURNAL, **75**, 5893 (1953).

(17) N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).

Anal. Calcd. for $C_{15}H_{13}NO_3S$: C, 62.70; H, 4.56; N, 4.88; S, 11.16. Found: C, 62.99; H, 4.59; N, 5.15; S, 11.19.

2,3-Dihydro-3-keto-1H-pyrido[3,2,1-kl]phenothiazine Sulfoxide (XI).—In a similar way this was prepared from 10.0 g. (0.04 mole) of the corresponding keto compound.[17] The product was recrystallized from 95% ethanol giving 7.0 g. (65%) of solid, m.p. 198–200°.

Anal. Calcd. for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.18; N, 5.20; S, 11.90. Found: C, 66.86; H, 4.07; N, 5.19; S, 11.95.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, ASSIUT UNIVERSITY]

Synthesis of Oxazolo-phenoxazines

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2-Aryl-5*H*-oxazolo[4,5-*b*]phenoxazines (II) were synthesized by heating 3-aminophenoxazone-2 (I) with aromatic aldehydes in the absence of solvents and basic catalysts. The oxazol-phenoxazines (II) were attacked by concentrated hydrochloric acid giving 2-hydroxy-3-aminophenoxazine hydrochloride (III). When III was heated with aromatic aldehydes, it was reconverted to the corresponding oxazolo-phenoxazines. The action of benzyl chloride on I gave 2-phenyl-5-benzyl-oxazolo[4,5-*b*]phenoxazine (VIII). This also was obtained by the action of benzyl chloride on 2-phenyl-5*H*-oxazolo[4,5-*b*]-phenoxazine. Mechanisms explaining the formation of II and VIII are discussed.

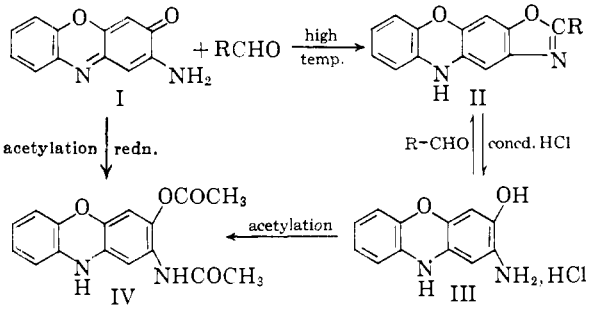
The remarkable antibacterial and antifungal activities of some oxazoles[1] has prompted us to synthesize new oxazoles. It was thought that the combination of an oxazole ring with a heterocyclic nucleus might increase these biological activities, and so the synthesis of previously unknown oxazolophenoxazines(II) was undertaken.

The route (chosen) for the synthesis involves the action of aldehydes on 3-aminophenoxazone-2 (I), to form an intermediate Schiff base which was expected to cyclize and rearrange forming oxazolo-phenoxazines (II). 3-Aminophenoxazone-2 (I) is known to be an oxidation product of *o*-aminophenol,[2] and it was conveniently prepared by oxidation of *o*-aminophenol with an equivalent amount of *p*-benzoquinone in alcohol.

The reaction between 3-aminophenoxazone-2 (I) and aldehydes was tried several times using the procedure usually applied to the preparation of oxazoles, *i.e.*, use of a suitable solvent and a basic catalyst[3]; however, the reaction did not proceed and the aminophenoxazone was recovered unchanged. It was discovered that by heating the reactants alone in the direct flame or better by refluxing them for a short time at the boiling point of the aldehyde, the required condensations were effected giving yellow products. The reaction was positive only with aromatic aldehydes, while aliphatic aldehydes failed to react even when heated in a sealed tube for a long time. The products showed strong fluorescence in different solvents and in concentrated sulfuric acid, a property which is usually exhibited by oxazoles. On investigation, the yellow compounds were found to be devoid of carbonyl groups or conjugated systems. This was also confirmed by the infrared absorption spectra which showed no characteristic bands for these groups, but a medium band was shown at 3340 $cm.^{-1}$, indicating a secondary amino group.[4,5]

These facts together with the analytical results were in full agreement with structure II originally proposed for these compounds.

The oxazolo-phenoxazines (II) were unstable in concentrated mineral acids, and when warmed with concentrated hydrochloric acid the oxazole ring was readily cleaved giving 2-hydroxy-3-amino-phenoxazine hydrochloride (III). This on acetylation gave a colorless diacetate (IV), identical with that obtained by reductive acetylation of I. When III was heated with aromatic aldehydes (but not aliphatic aldehydes), the corresponding oxazolo-phenoxazines were produced.



The mechanism of formation of the oxazolo-phenoxazines (II) from I and aromatic aldehydes apparently involves an aminoaldehyde condensation forming an intermediate Schiff base (V). This intermediate is expected to undergo electronic displacements across the conjugated double bonds with simultaneous cyclization forming a molecule of the type VI. The extra hydrogen atom attached to the oxazole ring in VI is probably transferred as a proton to the nitrogen atom in the phenoxazine nucleus thus forming a secondary amino group. This transfer is influenced by the polarity of the molecule VI. At this stage the molecule attains its stability with the formation of the oxazolo-phenoxazines (II) (*cf.* Scheme A).

The investigation was extended to the action of benzyl chloride and benzyl cyanide on 3-amino-

(1) U. S. Patent 2,630,381 Mar. 3, 1953; L. Katz, *et al.*, THIS JOURNAL, **75**, 712 (1953); *J. Org. Chem.*, **19**, 756 (1954).

(2) O. Fisher, *et al.*, *Ber.*, **27**, 2784 (1894); F. Hepp, *ibid.*, **28**, 297 (1895); Zincke and Heberbrand, *Ann.*, **226**, 61 (1884).

(3) C. W. C. Stein and A. R. Day, THIS JOURNAL, **64**, 2567 (1942); A. M. Osman, *ibid.*, **79**, 966 (1957).

(4) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methuen, London, 1954, p. 212.

(5) We wish to thank Prof. F. G. Baddar, Chem. Dept., Faculty of Science, Aln-Shams University, for the determination of the infrared absorption spectra.