2-*tert*-Butyl-10-(3-dimethylaminopropyl)-phenothiazine and Related Compounds[1]

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The thionation of 3-isopropyl-, 3-*tert*-butyl-, 3-(1,1-dimethylpropyl)-, and 4-*tert*-butyldiphenylamine gave 2-isopropyl-, 2-*tert*-butyl-, 2-(1,1-dimethylpropyl)-, and 3-*tert*-butylphenothiazine, respectively. In the presence of sodamide, these phenothiazines reacted with various dialkylaminoalkyl chlorides to give the corresponding 10-substituted derivatives. In a pharmacological comparison, 2-*tert*-butyl-10-(3-dimethylaminopropyl)-phenothiazine was more potent as a tranquilizing agent than the related derivatives of 2-chloro-, 2-methyl-, or 2-isopropylphenothiazine. Generally, 3-substituted-10-dimethylaminopropylphenothiazines are inactive; however, the 3-*tert*-butyl isomer appeared to be equipotent with the 2-chloro derivative.

As part of a research program on central nervous system depressants, we have synthesized several different series of *ar*-substituted 10-dialkylaminoalkyl phenothiazines.[2-5] The pharmacological properties of a number of these compounds have been reported.[6,7]

A continuation of this program has led to the synthesis of 10-dialkylaminoalkylphenothiazines with branched alkyl substituents, *e.g.*, the isopropyl, *tert*-butyl and 1,1-dimethylpropyl groups. This paper describes the synthesis of these novel derivatives and summarizes some of their pharmacological properties.

The condensation of *o*-chlorobenzoic acid with *m*-*tert*-butylaniline[8] in the Ullmann diphenylamine synthesis[9] led to 3-*tert*-butyldiphenylamine. The thionation of this with sulfur gave the key intermediate,

(1) Presented in part at the Thirteenth Meeting-in-Miniature, North Jersey Section of the American Chemical Society, January 30, 1961.

(2) H. L. Yale, *J. Am. Chem. Soc.*, **77**, 2270 (1955).

(3) H. L. Yale, F. Sowinski, and J. Bernstein, *ibid.*, **79**, 4375 (1957).

(4) H. L. Yale and F. Sowinski, *ibid.*, **80**, 1651 (1958).

(5) H. L. Yale and F. Sowinski, *ibid.*, **82**, 2039 (1960).

(6) J. J. Piala, J. P. High, G. L. Hassert, Jr., J. C. Burke, and B. N. Craver, *J. Pharmacol. Exptl. Therap.*, **127**, 55 (1959).

(7) J. P. High, G. L. Hassert, Jr., B. Rubin, J. J. Piala, J. C. Burke, and B. N. Craver, *Toxicol. Appl. Pharmacol.*, **2**, 540 (1960).

(8) M. S. Carpenter, W. M. Easter, and T. F. Wood, *J. Org. Chem.*, **16**, 586 (1951).

(9) F. Ullmann, *Ann.*, **355**, 312 (1907).

2-*tert*-butylphenothiazine. Subsequent reaction of this intermediate with the appropriate dialkylaminoalkyl halides in the presence of sodamide afforded the 2-*tert*-butyl-10-dialkylaminoalkylphenothiazines (II–VII) listed in Table I. A similar reaction of 2-*tert*-butylphenothiazine with 1-bromo-3-chloropropane, then condensation with 1-piperazinoethanol provided 2-[3-(2-*tert*-butyl-10-phenothiazinyl)-propyl]-1-piperazinoethanol (VIII). Acetyl chloride and VIII gave the acetate (IX).

An analogous synthetic sequence beginning with *m*-isopropylaniline[8] led to 2-isopropyl-10-(3-dimethylaminopropyl)-phenothiazine (I); in similar fashion, *m*-(1,1-dimethylpropyl)-aniline[10] gave the 2-(1,1-dimethylpropyl)-phenothiazines, XII and XIII. The use of *p*-*tert*-butylaniline[11] in this reaction scheme gave the 3-*tert*-butylphenothiazine derivatives, XIV and XV. The yields, physical constants, and analytical data for these derivatives and their salts are given in Table I.

The thionation of a 3-substituted diphenylamine can involve both the 2- and the 6-positions. Thus 3-chlorodiphenylamine,[12] 3-methylmercaptodiphenylamine,[13,14] 3-methyldiphenylamine,[12] 3-(trifluoromethyl)-diphenylamine,[3] and 3-(trifluoromethyl)-mercaptodiphenylamine[14] have been reported to give both 2- and 4-substituted phenothiazines. No 4-substituted isomers were found in the reaction mixtures from the thionation of 3-isopropyldiphenylamine, 3-*tert*-butyldiphenylamine, and 3-(1,1-dimethylpropyl)-diphenylamine, despite a careful workup of the reaction mixtures; only the 2-substituted products were obtained. The apparent failure to form any 4-substituted phenothiazines during thionation of diphenylamines with highly branched alkyl substituents in the 3-position must be attributed to the steric effects of these bulky groups.

Two oxidation products of 2-*tert*-butyl-10-(3-dimethylaminopropyl)-phenothiazine (III) were prepared. The *5-oxide* derivative (X) of III was obtained by heating an ethyl alcohol solution of the oxalate with one mole of hydrogen peroxide. Heating the free base of III in ethyl alcohol solution with two moles of hydrogen perox-

(10) J. Strating and H. J. Backer, *Rec. trav. chim.*, **62**, 57 (1943).

(11) D. Craig, *J. Am. Chem. Soc.*, **57**, 195 (1935).

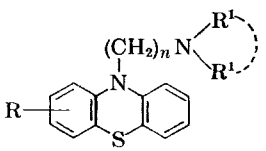
(12) P. Charpentier, P. Gaillot, R. Jacob, J. Gaudechon, and J. Buisson, *Compt. rend.*, **235**, 59 (1952).

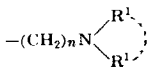
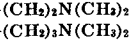
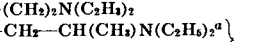
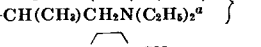
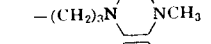
(13) J. P. Bourquin, G. Schwarb, G. Gamboni, R. Fischer, L. Ruesch, S. Guldiman, V. Theus, E. Schenker, and J. Renz, *Helv. Chim. Acta*, **41**, 1061 (1958).

(14) E. A. Nodiff, S. Lipschutz, P. N. Craig, and M. Gordon, *J. Org. Chem.*, **25**, 60 (1960).

TABLE I

2- AND 3-ALKYL-10-(*tert*-AMINOALKYL)-PHENOTHIAZINES AND THEIR DERIVATIVES



No.	Substituent R		Mol. formula	Yield, %	Boiling point °C.	Boiling point Mm.	Analyses, wt% Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
			Bases									
I	2-CH(CH$_3$)$_2$	—(CH$_2$)$_3$N(CH$_3$)$_2$	$C_{20}H_{26}N_2S$	44	213–215	1.2	73.57	73.52	8.02	7.76	..	..
II	2-C(CH$_3$)$_3$	—(CH$_2$)$_2$N(CH$_3$)$_2$	$C_{20}H_{26}N_2S$	59	192–195	0.5	73.57	73.31	8.02	7.53	..	..
III	2-C(CH$_3$)$_3$	—(CH$_2$)$_3$N(CH$_3$)$_2$	$C_{21}H_{28}N_2S$	84	196–198	0.4	74.06	74.61	8.28	8.08	..	..
IV	2-C(CH$_3$)$_3$	—(CH$_2$)$_2$N(C$_2$H$_5$)$_2$	$C_{22}H_{30}N_2S$	67	187–189	0.3	...	...	..	..	7.90	8.10
V	2-C(CH$_3$)$_3$	—CH$_2$—CH(CH$_3$)N(C$_2$H$_5$)$_2$[a]	$C_{23}H_{32}N_2S$	74	195–200	0.3	74.95	74.68	8.40	8.86	7.60	7.58
VI	2-C(CH$_3$)$_3$	—CH(CH$_3$)CH$_2$N(C$_2$H$_5$)$_2$[a]										
VII	2-C(CH$_3$)$_3$		$C_{24}H_{33}N_3S$	63	215–218	0.3	72.86	73.64	8.40	8.56	..	..
VIII	2-C(CH$_3$)$_3$		$C_{26}H_{36}N_3OS$	29	255–258	0.2	70.52	70.04	8.28	8.17	..	..
IX	2-C(CH$_3$)$_3$		$C_{27}H_{37}N_3O_2S$	42	.....	...	69.33	68.82	7.96	8.19	..	..
XI	2-C(CH$_3$)$_3$;5-O		$C_{21}H_{28}N_2O_2S\cdot 2H_2O$	40	[b,c]	...	62.32	62.22	7.96	7.58	6.92	6.83
XII	2-C(CH$_3$)$_2$C$_2$H$_5$	—(CH$_2$)$_3$N(CH$_3$)$_2$	$C_{22}H_{30}N_2S$	55	[d]	...	74.51	75.15	8.52	8.48	..	..
XIII	2-C(CH$_3$)$_2$C$_2$H$_5$		$C_{26}H_{37}N_3OS$	14	>250	0.4	71.02	71.73	8.48	8.22	..	..
XIV	3-C(CH$_3$)$_3$	—(CH$_2$)$_2$N(CH$_3$)$_2$	$C_{20}H_{26}N_2S$	49	182–185	0.2	73.57	72.82	8.08	7.57	..	..
XV	3-C(CH$_3$)$_3$	—(CH$_2$)$_3$N(CH$_3$)$_2$	$C_{21}H_{28}N_2S$	78	193–196	0.1	74.06	75.19	8.28	7.96	..	..

Salts

No.	Mol. formula	Yield,[p] %	M.p., °C.	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
I	$C_{20}H_{26}N_2S\cdot HCl$[c]	70	202–203	66.17	66.32	7.49	7.47	7.71	7.84
II	$C_{20}H_{26}N_2S\cdot HCl$[c]	84	230–231	66.17	65.97	7.49	7.26	7.71	7.97
III	$C_{21}H_{28}N_2S\cdot HCl$[c]	67	205–207	66.90	66.83	7.75	7.52	7.43	7.28
	$C_{21}H_{28}N_2S\cdot C_2H_2O_4$[e]		195–197	64.14	63.91	7.02	7.12	6.51	6.48
IV	$C_{22}H_{30}N_2S\cdot HCl$[f]	76	198–200	67.57	67.54	7.99	8.05	7.17	7.07
V	$C_{23}H_{32}N_2S\cdot HCl$[g,h]	60	189–190	...	...	..	..	6.92	7.13
VI	$C_{23}H_{32}N_2S\cdot HCl$[i,j]	3	137–138	...	...	..	..	6.92	6.98
VII	$C_{24}H_{34}N_2S\cdot 2HCl\cdot 0.5H_2O$[k,l]	68	252–253 dec.	60.36	60.50	7.60	7.72	8.80	8.80
	$C_{24}H_{34}N_2S\cdot 2C_2H_2O_4$	25	222–223 dec.	58.41	58.17	6.48	6.36	7.30	7.35
VIII	$C_{25}H_{36}N_2OS\cdot 2HCl\cdot 0.5H_2O$[m,n]	72	253–255	59.15	59.47	7.54	7.31	8.28	8.30
IX	$C_{27}H_{37}N_3O_2S\cdot 2HCl\cdot 0.5H_2O$[o,p,q]	42	225–227	58.99	59.22	7.33	7.21	7.64	7.76
X	$C_{21}H_{28}N_2OS\cdot C_2H_2O_4$[r]	56	213–215	61.85	62.18	6.77	6.56	6.27	6.36
XII	$C_{22}H_{30}N_2S\cdot HCl$[s,t]	27	177–178	67.57	66.00	7.96	7.76	7.16	6.89
XIII	$C_{26}H_{37}N_3OS\cdot 2HCl\cdot 0.5H_2O$[o]	44	209–210 dec.	59.87	59.72	7.73	7.62	8.05	8.41
XIV	$C_{20}H_{26}N_2S\cdot HCl$[u]	62	135–137	66.17	66.40	7.49	7.50	7.71	7.55
XV	$C_{21}H_{28}N_2S\cdot HCl$[g]	83	177–178	66.90	67.04	7.75	7.55	7.43	7.28

[a] The yield, boiling point and analyses are for the mixture of isomeric bases. This mixture was treated with gaseous hydrogen chloride and the two hydrochlorides separated by fractional crystallization. The assignment of structure to the two isomers was based on criteria previously discussed; see reference 3, p. 4376, footnote *c*. [b] This base is a crystalline solid, m.p. 149–150°. [c] Recrystallized from acetonitrile. [d] Base was not distilled but converted directly to the hydrochloride. [e] Recrystallized once from ethyl alcohol and once from *n*-propyl alcohol. [f] Recrystallized from dry benzene. [g] Recrystallized from dry toluene. [h] *Anal.* Calcd.: Cl, 8.75. Found: Cl, 8.51. [i] Recrystallized from Skellysolve V. [j] *Anal.* Calcd.: Cl, 8.75. Found: Cl, 8.54. [k] Recrystallized from acetonitrile–anhydrous ether. [l] *Anal.* Calcd.: total volatiles, 1.89. Found: total volatiles, 2.03. [m] Recrystallized from *n*-propyl alcohol. [n] Drying *in vacuo* for 2 hr. at 135° gave the anhydrous salt. *Anal.* Calcd.: C, 60.24; H, 7.48. Found: C, 59.80; H, 7.48. [o] Recrystallized from isopropyl alcohol. [p] *Anal.* Calcd.: total volatiles, 1.63. Found: total volatiles, 1.5. [q] Drying *in vacuo* for 2 hr. at 135° gave the anhydrous salt. *Anal.* Calcd.: C, 59.98; H, 7.27. Found: C, 59.65; H, 7.28. [r] Recrystallized from *n*-butyl alcohol. [s] Recrystallized from chlorobenzene. [t] *Anal.* Calcd.: Cl, 9.06. Found: Cl, 8.75. [u] Recrystallized from chlorobenzene–anhydrous ether. [v] The distilled bases were converted directly to their salts; the percentage yields given are those of the analytically pure materials. [w] The difficulty in some instances in obtaining good analytical data on the distilled bases is attributed to the tendency for unreacted phenothiazine to codistil. These bases were converted to their salts which were purified readily by recrystallization and were now in a practical form for pharmacological evaluation.

ide resulted in the formation of the *N-5-dioxide* derivative, XI.[3]

Pharmacology.—The 10-dialkylaminoalkylphenothiazines reported in this paper were evaluated as tranquilizing agents in a screening procedure which has already been reported from these Laboratories.[6] The pharmacological data relating to these compounds are given in Table II along with comparable data for chloropromazine[6] and 10-(3-dimethylaminopropyl)-2-methylphenothiazine.[15]

A comparison of the tranquilization ratings of three key compounds was of considerable interest. Surprisingly, 10-(3-dimethylaminopropyl)-2-isopropylphenothiazine (I) was less potent than the corresponding 2-methyl derivative. However, the apparent trend was reversed with 2-*tert*-butyl-10-(3-dimethylaminopropyl)-phenothiazine (III) which was 3–4 times as potent as chloropromazine. The activity found with 3-*tert*-butyl-10-(3-dimethylaminopropyl)-phenothiazine (XV) was also unexpected in that, generally, 3-substituted-10-dimethylaminopropylphenothiazines, such as the chloro and the trifluoromethyl derivatives, are inactive; however, in the monkey, the 3-*tert*-butyl isomer appeared to be as potent as chloropromazine.

Acknowledgment.—The authors are indebted to Dr. Jack Bernstein for his interest and encouragement and for the many helpful and stimulating discussions during the course of this investigation. The authors also are indebted to Mr. J. F. Alicino and his associates for the microanalytical data. Dr. Nettie Coy and Miss Barbara Keeler determined the infrared spectra and aided in their interpretation.

Experimental Part

All melting and boiling points are uncorrected.

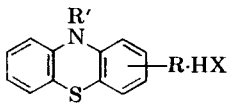
The procedure described below for 2-*tert*-butyl-10-(3-dimethylaminopropyl)-phenothiazine is illustrative and represents the method used in the preparation of the related 2-isopropyl-, 2-(1,1-dimethylpropyl)- and 3-*tert*-butylphenothiazine derivatives.

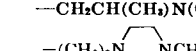
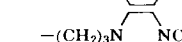
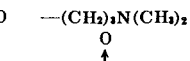
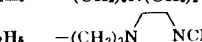
2-*tert*-Butyl-10-(3-dimethylaminopropyl)-phenothiazine (III). N-(*m*-*tert*-Butylphenyl)-anthranilic Acid.—To a stirred solution of 335 g. (7.7 moles) of flake sodium hydroxide in 7700 ml. of *n*-amyl alcohol at 50–60° was added 1205 g. (7.7 moles) of *o*-chlorobenzoic acid, 1042 g. (7.0 moles) of *m*-*tert*-butylaniline, and 70 g. of copper powder. The mixture was heated rapidly to 85–90° when a vigorous reaction took place. After the reaction subsided, the mixture was heated under reflux for 2 hr., cooled, made alkaline and steam distilled. The residual

(15) P. Viaud, *J. Pharm. and Pharmacol.*, **6**, 361 (1954).

TABLE II[a]

PHARMACOLOGICAL DATA



No.	R	R′	HX	Acute toxicity 5 day in mice LD50	Median dose inhibiting the unconditioned and conditioned avoidance responses in the rat I.P., mg./kg. UD50	CD50	UD50/CD50	Tranquilization rating in the rhesus monkey, P.O. mg./kg. Dose	Score
	2-Cl	—$(CH_2)_3N(CH_3)_2$	HCl	*b*...	16.5	5.5	3.0	10	1–2
	2-CH_3	—$(CH_2)_3N(CH_3)_2$	HCl	...	64.0	19.5	3.3	20	2
								10	0
I	2-$CH(CH_3)_2$	—$(CH_2)_3N(CH_3)_2$	HCl	...	27.0	17.1	1.6	20	0
								80	0
II	2-$C(CH_3)_3$	—$(CH_2)_3N(CH_3)_2$	HCl	100	138	76	1.8	...	...
III	2-$C(CH_3)_3$	—$(CH_2)_3N(CH_3)_2$	HCl	84	85	31	2.7	10	3–4
IV	2-$C(CH_3)_3$	—$(CH_2)_2N(C_2H_5)_2$	HCl	200	>200	>200	...	...	...
V	2-$C(CH_3)_2$	—$CH_2CH(CH_3)N(C_2H_5)_2$	HCl	...	>120	>120	...	...	...
VIII	2-$C(CH_3)_3$		2HCl	...	5.1	2.1	2.4	...	...
IX	2-$C(CH_3)_3$		2HCl	...	5.9	2.1	2.8	...	...
X	2-$C(CH_3)_3$,5-O	—$(CH_2)_3N(CH_3)_2$	$C_2H_2O_4$	120	118	84	1.4	...	...
XI	2-$C(CH_3)_3$,5-O			85	>40	>40	...	...	...
XII	2-$C(CH_3)_2C_2H_5$	—$(CH_2)_3N(CH_3)_2$	HCl	75–100	89	36–52	1.7–2.5	...	...
XIII	2-$C(CH_3)_2C_2H_5$		2HCl	92	>14	5.9	>2.4	...	...
XIV	3-$C(CH_3)_3$	—$(CH_2)_3N(CH_3)_2$	HCl	...	225	205	1.1	40	0
XV	3-$C(CH_3)_3$	—$(CH_2)_3N(CH_3)_2$	HCl	62	...	...	...	20	3

[a] We are indebted to the Pharmacology Section of the Squibb Institute for Medical Research for these data. [b] The symbol ... denotes that no data are available.

liquid then was filtered while hot, the filtrate cooled, and the pH adjusted to 6.0. Filtration of the precipitated solid gave 1910 g. of material, m.p. 128–130°, suitable for use in the next step. The analytical sample was recrystallized from ligroin and melted at 151–153°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.80; H, 7.11. Found: C, 75.81; H, 7.03.

3-*tert*-Butyldiphenylamine.—A stirred mixture of 1910 g. of the crude N-(*m*-*tert*-butylphenyl)-anthranilic acid and 30 g. of copper powder was heated under nitrogen in an oil bath from 200° initially to a final temperature of 270°, during 3 hr. The cooled mass was extracted with ether, the ether extract washed with 5% aqueous sodium hydroxide, dried, concentrated, and the residue distilled to give 1159 g. of a colorless oil (73% yield based on *m*-*tert*-butylaniline), b.p. 136–138° (0.03 mm.)

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.27; H, 8.49. Found: C, 85.03; H, 8.31.

2-*tert*-Butylphenothiazine.—A mixture of 135 g. (0.6 mole) of 3-*tert*-butyldiphenylamine, 38.5 g. (1.2 moles) of sulfur, and 4.4 g. of iodine was immersed in an oil bath preheated to 125° and heated rapidly under nitrogen to 145° (reaction temperature). After 45 min. the reaction mixture was cooled partially and 250 ml. of boiling toluene added. The toluene solution was heated to boiling, treated with Darco and Hyflo Super-cel, and filtered. The product separated on cooling and was recrystallized from heptane to give 108.8 g. (71% yield) of cream colored platelets, m.p. 163–165°. The analytical sample was recrystallized additionally from ethyl alcohol, m.p. 166–167°. In the infrared, this compound showed strong absorption at 12.27 μ, identifying it as the 2- isomer.[16,17]

Anal. Calcd. for $C_{16}H_{17}NS$: C, 75.24; H, 6.75. Found: C, 75.45; H, 6.27.

2-*tert*-Butyl-10-(3-dimethylaminopropyl)-phenothiazine.—A mixture of 19.1 g. (0.075 mole) of 2-*tert*-butylphenothiazine, 3.2 g. (0.082 mole) of sodamide and 400 ml. of dry toluene was stirred and heated under reflux in an atmosphere of nitrogen for 2 hr., cooled, 88 ml. (0.1 mole) of a 1.14 *M* toluene solution of 3-dimethylaminopropyl chloride added during 30 min., and heating under reflux resumed for an additional 3 hr. The mixture was filtered, cooled, and extracted with three 250 ml. portions of 5% hydrochloric acid. The acid extracts were combined, washed with ether, made alkaline, and the base extracted into ether. After drying, the ether extract was concentrated and the residue distilled to give 21.4 g. (84% yield) of the *base*, b.p. 196–198° (0.4 mm.).

To an ice-cooled solution of the *base* in 250 ml. of anhydrous ether was added with stirring a slight excess of 4 *N* ethereal hydrogen chloride. The precipitate was filtered, dried *in vacuo* and recrystallized from chlorobenzene to give 15.7 g. (67% yield) of the hydrochloride, m.p. 205–206°.

4-[3-(2-*tert*-Butyl-10-phenothiazinyl)-propyl]-1-piperazinoethanol (VIII). 2-*tert*-Butyl-10-(3-chloropropyl)-phenothiazine.—This product was obtained by a method similar to that described[5] for the preparation of the corresponding 2-trifluoromethyl derivative. The reaction between 51.0 g. (0.20 mole) of 2-*tert*-butylphenothiazine, 47.2 g. (0.30 mole) of 1-bromo-3-chloropropane, and 9.3 g. (0.24 mole) of sodamide in 750 ml. of dry toluene gave 32.6 g. (49% yield) of a

(16) N. L. Smith, *J. Org. Chem.*, **15**, 1125 (1950).
(17) A. Roe and W. F. Little, *ibid.*, **20**, 1577 (1955).

product, b.p. 240–244° (0.6 mm.), which contained a small amount of unreacted 2-*tert*-butylphenothiazine.[5] This product (32.6 g., 0.098 mole) reacted further with 39.2 g. (0.03 mole) of 1-piperazinoethanol., 15.0 g. of sodium iodide and 600 ml. of methyl ethyl ketone to give 11.9 g. of VIII. To a cooled, stirred solution of 6.2 g. (0.015 mole) of VIII in 50 ml. of anhydrous ether was added, dropwise, 8.0 ml. (0.031 mole) of 3.9 *N* ethereal hydrogen chloride. The granular material which formed was heated to boiling in 50 ml. of acetone, the mixture cooled, and filtered to give 6.7 g. of crude *dihydrochloride hemihydrate*, m.p. 247–249° (dec.). A recrystallization from *n*-propyl alcohol gave 5.3 g. of pure product, m.p. 253–255° (dec.).

4-[3-(2-*tert*-Butyl-10-phenothiazinyl)-propyl]-1-piperazinoethyl Acetate Ester (IX).—To a stirred, ice cooled solution of 5.0 g. (0.012 mole) of VIII in 30 ml. of dry chloroform was added, dropwise, a solution of 1.1 g. (0.014 mole) of acetyl chloride in 10 ml. of dry chloroform. The cooling bath was removed, the mixture stirred for 30 min., made acid to congo red with ethereal hydrogen chloride, and the solid filtered. Recrystallization from isopropyl alcohol gave 4.9 g. of dihydrochloride hemihydrate.

2-*tert*-Butyl-10-(3-dimethylaminopropyl)-phenothiazine-5-oxide Monooxalate Salt (X).—A solution of 40.0 g. (0.12 mole) of III in acetonitrile was treated with an acetonitrile solution of 10.8 g. (0.12 mole) of oxalic acid and the product recrystallized once from ethyl alcohol and once from *n*-propyl alcohol to give the pure oxalate, m.p. 195–197°. A mixture of 8.6 g. (0.02 mole) of this oxalate, 2.3 g. (0.026 mole) of 30% hydrogen peroxide and 125 ml. of ethyl alcohol was heated under reflux for 16 hr., clarified by filtration with Hyflo Super-cel, cooled, and the crude 5-oxide derivative filtered. Recrystallization from 1-butanol gave 5.0 g. of X, m.p. 213–215°.

2-*tert*-Butyl-10-(3-dimethylaminopropyl)-phenothiazine-*N*,5-dioxide Dihydrate (XI).—To 8.5 g. (0.025 mole) of III was added 125 ml. of isopropyl alcohol, and 4.4 g. (0.05 mole) of 30% hydrogen peroxide, the mixture heated under reflux for 16 hr., and concentrated. The residual oil slowly crystallized during vacuum desiccation. Recrystallization from acetonitrile gave 3.2 g. of XI as large white plates, m.p. 149–150°.

10-(3-Dimethylaminopropyl)-2-isopropylphenothiazine (I).—The preparation of *m*-isopropylaniline was patterned after the procedure of Carpenter *et al.*[8] The yields, physical constants and analytical data of the intermediates corresponding to those in the synthesis of 2-*tert*-butyl-10-(3-dimethylaminopropyl)-phenothiazine are given.

N-(*m*-Isopropylphenyl)-anthranilic Acid.—(85% yield), m.p. 120–121°.

Anal. Calcd. for $C_{16}H_{17}NO_2$: C, 75.26; H, 6.71. Found: C, 75.28; H, 6.47.

3-Isopropyldiphenylamine.—(74% yield), b.p. 146–149° (1.5–2.0 mm.).

Anal. Calcd. for $C_{15}H_{17}N$: C, 85.26; H, 7.74. Found: C, 85.02; H, 8.22.

2-Isopropylphenothiazine.—(47% yield), m.p. 152–153°, after recrystallization from heptane. This compound showed a strong peak in the infrared at 12.25 μ identifying it as the 2-isomer.[16,17]

Anal. Calcd. for $C_{15}H_{15}NS$: C, 74.64; H, 6.26; N, 5.80. Found: C, 74.50; H, 6.06; N, 5.82.

10-(3-Dimethylaminopropyl)-2-(1,1-dimethylpropyl)-phenothiazine (XII).—1,1-

Dimethylpropylbenzene,[18] by a synthetic sequence similar to that employed for the preparation of *m*-isopropylaniline, gave 3-(1,1-dimethylpropyl)-aniline.[19] The intermediates listed were obtained by the procedure already described for 2-*tert*-butyl-10-(3-dimethylaminopropyl)-phenothiazine, and are given along with yields, physical constants, and analytical data.

N-[*m*-(1,1-Dimethylpropyl)-phenyl]-anthranilic Acid.—(92% yield), m.p. 105–107°.

Anal. Calcd. for $C_{18}H_{21}NO_2$: C, 76.68; H, 7.47. Found: C, 76.58; H, 7.39.

3-(1,1-Dimethylpropyl)-diphenylamine.—(70% yield), b.p. 166–169° (1.4 mm.).

Anal. Calcd. for $C_{17}H_{21}N$: C, 85.30; H, 8.84. Found: C, 85.33; H, 8.60.

2-(1,1-Dimethylpropyl)-phenothiazine.—Extraction of the cooled thionation mixture with boiling petroleum ether (b.p. 120–140°) gave 83% of black needles, m.p. 108–110°. The color could not be removed by recrystallization; consequently, this solid was distilled and the middle fraction, b.p. 200–203 (1.4 mm.) recrystallized from ligroin (b.p. 66–75°) to give the pure colorless product in 32% yield, m.p. 117–118°. Chromatography on alumina gave the same material but in only 28% yield. In the infrared, this phenothiazine showed strong absorption at 12.35 μ, identifying it as the 2-isomer.[16,17]

Anal. Calcd. for $C_{17}H_{19}N_2S$: C, 75.79; H, 7.10. Found: C, 76.16; H, 7.06.

3-*tert*-Butyl-10-(3-dimethylaminopropyl)-phenothiazine (XV). ***p*-*tert*-Butylaniline.**—*p*-*tert*-Butylacetanilide[3] (217 g., 1.1 moles) was heated under reflux for 3 hr. with 100 ml. of water, 300 ml. of ethyl alcohol and 500 ml. of concentrated hydrochloric acid, the mixture cooled, and the product filtered; the concentrated mother liquors gave additional product. The combined yield was 233.4 g. of air dried hydrochloride, m.p. 268–270° (melting point bath preheated to 250°).

Anal. Calcd. for $C_{10}H_{15}N \cdot HCl$: Cl, 19.09. Found: Cl, 18.73

The hydrochloride, dissolved in hot water, was decomposed with solid potassium carbonate, extracted with ether, the ether solution dried, and distilled to give 109.4 g. (73% yield) of *p*-*tert*-butylaniline,[19] b.p. 86–89° (5 mm.)

The preparation of the 3-*tert*-butylphenothiazines involved a procedure similar to that described before for the 2-*tert*-butyl derivative. The yields, physical constants and analyses for the intermediate compounds are given.

N-(*p*-*tert*-Butylphenyl)-anthranilic Acid.—(56% yield), m.p. 205–206°.

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.80; H, 7.11. Found: C, 75.59; H, 7.17.

4-*tert*-Butyldiphenylamine.—(87% yield), m.p. 65–66°, b.p. 150–152° (2.5 mm.).

Anal. Calcd. for $C_{16}H_{19}N$: C, 85.27; H, 8.49. Found: C, 85.26; H, 8.51.

3-*tert*-Butylphenothiazine.—(44% yield), m.p. 156–157°, after recrystallization from ethyl alcohol.

Anal. Calcd. for $C_{16}H_{17}NS$: C, 75.24; H, 6.75. Found: C, 75.54; H, 6.48.

1-(3-Chloropropyl)-4-methylpiperazine and Dihydrochloride, Hemihydrate.—To an ice-cooled solution of 157.5 g. (1 mole) of 1-bromo-3-chloropropane in 750 ml. of anhydrous ether was added while stirring a solution of 200.3 g. (2 moles) of 1-methylpiperazine in 250 ml. of anhydrous ether during a period of 1 hr. The

(18) M. Inatome, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, **74**, 292 (1952).

(19) Craig prepared this compound by the nitration and subsequent reduction of *tert*-butylbenzene.

mixture was then heated under reflux for 2.5 hr., kept 16 hr.; the solid filtered, the filtrate cooled, and extracted with 750 ml. of cold 20% hydrochloric acid. With continued ice-cooling, the acid extract was made alkaline with solid potassium carbonate and the base extracted with ether. Concentration of the dried ether extract and distillation of the residue gave 142.3 g. (81% yield) of the *base*, b.p. 57–60° (1 mm.), $n^{22}D$ 1.4773.

Anal. Calcd. for $C_8H_{17}ClN_2$: Cl, 20.08. Found: Cl, 20.64.

A solution of the *base*, in ether, was cooled, treated with a slight excess of ethereal hydrogen chloride, the solid filtered, and recrystallized from isopropyl alcohol to give the dihydrochloride hemihydrate, m.p. 258–260°.

Anal. Calcd. for $C_8H_{17}ClN_2 \cdot 2HCl \cdot 0.5H_2O$: Cl (total), 41.13. Found: Cl (total), 41.13, 41.26.

Some Analogs of Chlordiazepoxide

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Among some analogs of chlordiazepoxide that were prepared, only 2-amino-7-chloro-5-phenyl-3H-1,4-benzodiazepine and its 2-methylamino homolog showed activity approaching that of chlordiazepoxide.

7-Chloro-2-methylamino-5-phenyl-3H-1,4-benzodiazepine 4-oxide was disclosed by Sternbach[1] as the product of the action of methylamine upon 6-chloro-2-chloromethyl-4-phenylquinazoline 3-oxide. This compound subsequently has been used successfully as an antianxiety agent (chlordiazepoxide). In order to determine in our laboratories the effect of structural changes on the activity, we have prepared a number of related compounds. Those compounds not reported in the recent publications of Sternbach, Kaiser, and Reeder[2] and Sternbach and Reeder[3] are listed in Tables I and II.

All of the compounds were prepared by known methods. We found, as did Sternbach and Reeder,[3] that secondary amines and

(1) L. H. Sternbach, U. S. Patent 2,893,992 (1959).
(2) L. H. Sternbach, S. Kaiser and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).
(3) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).