m.p. 149–151°, and 0.28 g. (15%) of crude tetraphenylsilane, m.p. 193–208°, which after recrystallization from benzene gave 0.18 g. (10%) of pure tetraphenylsilane, m.p. 230–232°, all products identified by mixed melting point.

Acknowledgment.—The author is indebted to N. Wolfish and M. Gold for technical assistance, to Dr. Henry Gilman and the Institute for Atomic Research, Iowa State College, for the infrared spectrum and to the National Research Council of Canada for a grant supporting this research.

TORONTO, CANADA

[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

10-(3-Dimethylaminopropyl)-2-(Trifluoromethyl)-phenothiazine Hydrochloride (VESPRIN[1]) and Related Compounds. I

BY HARRY L. YALE, FRANCIS SOWINSKI AND JACK BERNSTEIN

RECEIVED MARCH 18, 1957

The thionation of 3-(trifluoromethyl)-diphenylamine has yielded 2- and 4-(trifluoromethyl)-phenothiazine. These two nuclei have been allowed to react with various dialkylaminoalkyl chlorides in the presence of sodamide to give 10-dialkylaminoalkyl-2- and 4-(trifluoromethyl)-phenothiazine. Hydrogen peroxide has converted these compounds to various oxygenated derivatives. An improved procedure is described for the preparation of 3-(trifluoromethyl)-phenothiazine. Since this nucleus did not react with dimethylaminopropyl chloride in the presence of sodamide, an indirect procedure was used to prepare the 10-(3-dimethylaminopropyl) derivative.

We have for several years been interested in variously substituted phenothiazine derivatives[2] and wish now to report on a series of 10-dialkylaminoalkyl-2-, -3- and -4-(trifluoromethyl)-phenothiazines and their oxygenated derivatives. Several of these compounds have shown good specificity and high potency as ataractic agents in laboratory animals[3] and are now undergoing clinical evaluation.

The thionation of 3-(trifluoromethyl)-diphenylamine should lead to the formation of both 2-(trifluoromethyl)-phenothiazine and 4-(trifluoromethyl)-phenothiazine. From such a reaction, however, Smith[4] isolated only one (trifluoromethyl)-phenothiazine. This compound showed a deep band in the infrared at 12.17 μ, an absorption band not seen in the spectrum of phenothiazine itself. Since the infrared spectra of asymmetrical trisubstituted benzenes show a characteristic deep band in the region 12.0–12.5 μ while vicinal trisubstituted benzenes show a characteristic deep band in the region 12.5–13.15 μ, Smith concluded that his product was 2-(trifluoromethyl)-phenothiazine. This method of differentiating isomers in monosubstituted phenothiazines received additional support in the observation of Roe and Little[5] that 3-(trifluoromethyl)-phenothiazine, prepared by an unambiguous synthesis, showed a deep band in the infrared at 12.2 μ.

The work of Charpentier[6] has demonstrated that the thionation of 3-substituted diphenylamines, *e.g.*, 3-methyldiphenylamine, leads to 2- and 4-substituted phenothiazines; the less soluble, higher melting isomer (m.p. 187–188°) when heated with copper bronze gave 2-methylcarbazole, while the more soluble, lower melting isomer (m.p. 114–115°) gave 4-methylcarbazole.

We have re-examined the thionation of 3-(trifluoromethyl)-diphenylamine, and have isolated both 2-(trifluoromethyl)-phenothiazine, m.p. 188–189°, in 45% yield, and the hitherto unreported 4-(trifluoromethyl)-phenothiazine, m.p. 72–73° in 32% yield. It is of interest that the latter isomer showed a strong band at 12.7 μ, as anticipated, since it corresponds to a *vicinal* substituted benzene.

3-(Trifluoromethyl)-phenothiazine was prepared in one step in 52% yield by Roe and Little[5] *via* the Smiles rearrangement of 2-formamido-2′-nitro-4′-(trifluoromethyl)-diphenyl sulfide. Based on our own experience, we prefer the two step modification of the Smiles rearrangement, which employed the *2-acetamido derivative* and which gave a 91% yield over-all.

The reactions of 2- and 4-(trifluoromethyl)-phenothiazine with various dialkylaminoethyl chlorides and dialkylaminopropyl chlorides in toluene or xylene, in the presence of sodamide, gave the desired 10-substituted derivatives in good yields. The reaction of 3-(trifluoromethyl)-phenothiazine with dimethylaminopropyl chloride under the same conditions was unsuccessful. Instead of the usual dark brown colored reaction mixtures, deep violet colored solutions were obtained, which, even after prolonged reflux periods, when cooled and hydrolyzed with water became colorless and when worked up in the usual manner yielded only unreacted 3-(trifluoromethyl)-phenothiazine. It became necessary to use the indirect procedure outlined below which gave the desired product.

2-(Trifluoromethyl)-10-phenothiazinepropionitrile[7] and lithium aluminum hydride gave 10-(3-aminopropyl)-2-(trifluoromethyl)-phenothiazine.

The preparation of 10-(4-dimethylaminobutyl)-2-(trifluoromethyl)-phenothiazine followed the sequence of reactions shown below, employing 4-

(1) VESPRIN is a trademark of the Olin Mathieson Chemical Corporation.

(2) H. L. Yale, THIS JOURNAL, **77**, 2270 (1955).

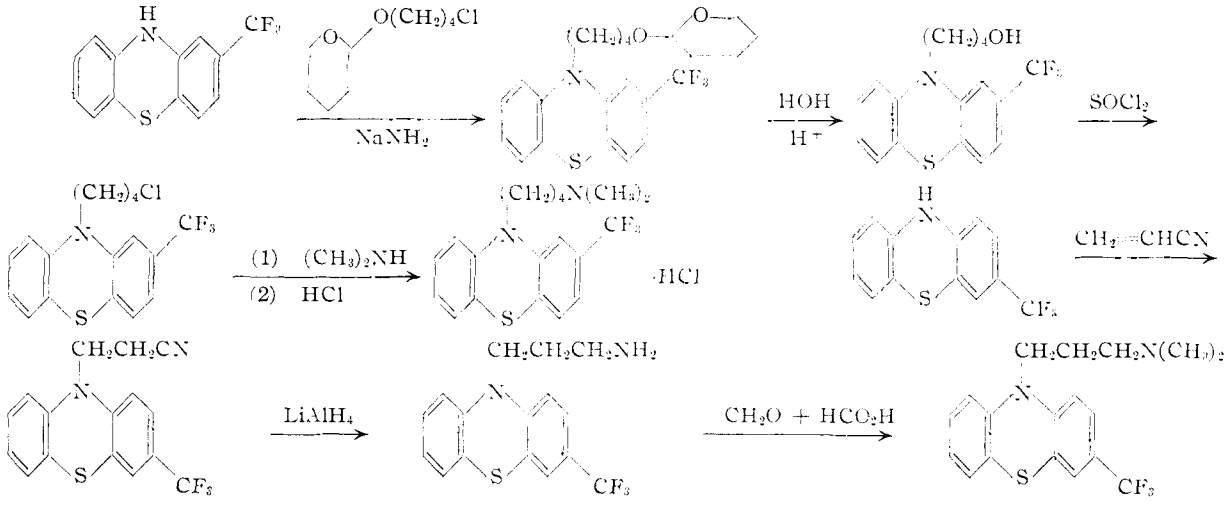
(3) The tranquilizing activity of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine hydrochloride was reported by J. C. Burke, H. L. Yale, G. L. Hassert and J. P. High and by J. J. Piala, J. P. High, K. Greenspan and J. C. Burke at the 1956 Meeting of The American Society for Pharmacology and Experimental Therapeutics at French Lick Springs, Indiana, November 8–10, 1956.

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

(5) A. Roe and W. F. Little, *ibid.*, **20**, 1577 (1955), have discussed the infrared spectra of this compound as well as a number of other fluorine substituted phenothiazines.

(6) P. Charpentier, P. Gailliot, R. Jacob, J. Gaudechon and J. Buisso, *Compt. rend.*, **235**, 59 (1952).

(7) N. L. Smith, *J. Org. Chem.*, **16**, 415 (1951).



chlorobutyl-2-tetrahydropyranyl ether as the side chain precursor; several of the intermediates were high boiling viscous oils which were difficult to obtain analytically pure, although the final product, phenothiazine some cleavage to 2-(trifluoromethyl)-phenothiazine occurred. This is not surprising since Charpentier[9] found that 10-(2-dimethylaminopropyl)-phenothiazine and boiling 48% hydro-

TABLE I

10-DIALKYLAMINOALKYL-2-(TRIFLUOROMETHYL)-PHENOTHIAZINES AND THEIR DERIVATIVES

Side chain	Mol. formula	Yield, %	Boiling point °C.	Mm.	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Base										
$-(CH_2)_3NH_2$	$C_{16}H_{15}F_3N_2S$	42	176–178	0.6			4.31[a]			4.30[a]
$-(CH_2)_2N(CH_3)_2$	$C_{17}H_{17}F_3N_2S$	84	[b]							
$-(CH_2)_3N(CH_3)_2$	$C_{18}H_{19}F_3N_2S$	93	162–164	.4			7.94			8.16
$-CH_2CH(CH_3)N(CH_3)_2$[c]	$C_{18}H_{19}F_3N_2S$	20	166–169	.3			7.94			8.00
$-(CH_2)_4N(CH_3)_2$	$C_{19}H_{21}F_3N_2S$	82	[b]							
$-(CH_2)_2N(C_2H_5)_2$	$C_{19}H_{21}F_3N_2S$	56	171–173	.5	62.27	5.78		62.16	5.80	
$-(CH_2)_3N(C_2H_5)_2$	$C_{20}H_{23}F_3N_2S$	73	167–170	.4	63.16	6.09		63.18	6.13	
$-(CH_2)_3-N<\begin{matrix}CH_2-CH_2\\ \\ CH_2-CH_2\end{matrix}$	$C_{20}H_{21}F_3N_2S$	100	[b]		63.46	5.59		63.92	5.70	
Salts										
Mol. formula			M.p., °C.							
$C_{16}H_{15}F_3N_2S\cdot HCl$[d]		48	161–162		53.25	4.47	7.76	53.13	4.70	7.82
$C_{17}H_{17}F_3N_2S\cdot HCl$[e]		70	245–246		54.76	4.32	7.51	54.83	4.68	7.39
$C_{18}H_{19}F_3N_2S\cdot HCl$[e,f]		61	173–174		55.59	5.18	7.20	55.53	5.33	7.14
$C_{18}H_{19}F_3N_2S\cdot HCl$[g]		41	224–225 dec.		55.59	5.18	7.20	55.53	5.36	7.38
$C_{19}H_{21}F_3N_2S\cdot HCl$[h]		48	153–154		56.64	5.50	6.95	56.89	5.42	6.89
$C_{19}H_{21}F_3N_2S\cdot HCl$[i]		74	160–162		56.64	5.50	6.95	56.36	5.58	6.91
$C_{20}H_{23}F_3N_2S\cdot HCl$[g]		79	163–165		57.62	5.56	6.72	57.44	5.94	7.07
$C_{20}H_{23}F_3N_2S\cdot C_2H_2O_4$[j]		100	192–194 dec.				5.96			5.96
$C_{20}H_{21}F_3N_2S\cdot HCl$[k]		32	173–174		57.89	5.34	6.75	58.15	5.35	6.75

[a] Titratable N with $HClO_4$ in glacial acetic acid. [b] Base was not distilled but converted directly to hydrochloride. [c] The 2-dimethylaminopropyl side chain is tentatively assigned to this compound by analogy with similar compounds prepared by P. Charpentier, *et al.*, *Compt. rend.*, **225**, 306 (1947); **232**, 415 (1951), by the reaction of phenothiazine with 1-dimethylamino-2-chloropropane. As shown by Charpentier and also by N. D. Edge and W. R. Wragg, *J. Pharm. Pharmacol.*, **5**, 279 (1953), this reaction leads to two isomers. The isomer formed in the larger quantity has the 2-dimethylaminopropyl side chain and can be separated from the isomeric product with the 2-dimethylamino-1-methylethyl side chain by fractional crystallization of their hydrochlorides. The less soluble hydrochloride has the 2-dimethylaminopropyl side chain. [d] Recrystallized successively from dry chlorobenzene and from absolute isopropyl alcohol. [e] Recrystallized from dry chlorobenzene. [f] Recrystallized from acetonitrile. [g] Recrystallized from absolute ethanol-ether. [h] Recrystallized from dry toluene. [i] Recrystallized from dry benzene. [j] Recrystallized from water. [k] Recrystallized from dry xylene.

as the hydrochloride, was easily purified.[8] It was observed that during the reaction of thionyl chloride with 10-(4-hydroxybutyl)-2-(trifluoromethyl)-

(8) This procedure is very briefly outlined in U. S. Patent 2,645,640 (July 14, 1953) as the method used to prepare 2-chloro-10-(4-dimethylaminobutyl) phenothiazine.

bromic acid readily gave phenothiazine and 2-dimethylaminopropyl bromide, hydrobromide.

These 10-dialkylaminoalkyl-2- and 4-(trifluoromethyl)-phenothiazines were obtained as viscous

(9) P. Charpentier, P. Gailliot and J. Gaudechon, *Compt. rend.*, **232**, 2232 (1950).

TABLE II

10-DIALKYLAMINOALKYL-3-(TRIFLUOROMETHYL)-PHENOTHIAZINES AND THEIR DERIVATIVES

Side chain	Mol. formula	Yield, %	Boiling point °C.	Mm.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Base										
$-(CH_2)_3NH_2$	$C_{18}H_{15}F_3N_2S$	33	175–178	0.5			4.31[a]			4.64
$-(CH_2)_3N(CH_3)_2$	$C_{18}H_{19}F_3N_2S$	35	168–171	.3	61.34	5.43		62.11	5.41	
Salts										
Mol. formula			M.p., °C.							
$C_{18}H_{19}F_3N_2S\cdot HCl$[b]		66	140–141		55.59	5.18	7.20	55.68	5.35	7.32

[a] Titratable N with $HClO_4$ in glacial acetic acid. [b] Recrystallized from dry toluene.

TABLE III

10-DIALKYLAMINOALKYL-4-(TRIFLUOROMETHYL)-PHENOTHIAZINES AND THEIR DERIVATIVES

Side chain	Mol. formula	Yield, %	Boiling point °C.	Mm.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Base										
$-(CH_2)_3N(CH_3)_2$	$C_{18}H_{19}F_3N_2S$	79	169–172	0.3	61.34	5.43		61.27	5.16	
$CH_2CH(CH_3)N(CH_3)_2$	$C_{18}H_{19}F_3N_2S$	77	172–175	.4	61.34	5.43		62.38	5.37	
$-(CH_2)_3-N<\begin{matrix}CH_2-CH_2\\ \vert\quad\vert\\ CH_2-CH_2\end{matrix}$	$C_{20}H_{21}F_3N_2S$	41	176–179	.3	63.46	5.59		63.81	5.63	
Salts										
Mol. formula			M.p., °C.							
$C_{18}H_{19}F_3N_2S\cdot HCl$[a]		61	146–147		55.59	5.18	7.20	55.53	5.10	7.41
$C_{18}H_{19}F_3N_2S\cdot HCl$[b]		78	196–197		55.59	5.18	7.20	55.58	5.09	6.93
$C_{20}H_{21}F_3N_2S\cdot HCl$[c]		35	148–149		57.89	5.34	6.75	57.99	5.36	6.98

[a] Recrystallized from dry chlorobenzene–ether. [b] Recrystallized from dry chlorobenzene. [c] Recrystallized from dry acetone.

liquids which could be distilled *in vacuo* without decomposition; they formed crystalline hydrochlorides and acid oxalates. Their properties along with analytical data are summarized in Tables I, II and III.

It was of interest that 10-dimethylaminopropyl-2-(trifluoromethyl)-phenothiazine hydrochloride showed a deep band at 12.2 μ, 10-dimethylaminopropyl-3-(trifluoromethyl)-phenothiazine hydrochloride a deep band at 12.3 μ and 10-dimethylaminopropyl-4-(trifluoromethyl)-phenothiazine a deep band at 12.6 μ.

The 10-dialkylaminoalkyl-2- and 4-(trifluoromethyl)-phenothiazines were converted to the **5-oxide derivatives** by refluxing the oxalate in ethanol with one molar equivalent of 30% hydrogen peroxide. The N,5-dioxides were obtained by refluxing the base in ethanol with two molar equivalents of 30% hydrogen peroxide. To prepare the 5,5-dioxides, the 2- and 4-(trifluoromethyl)-phenothiazines were first converted to the **10-acetyl derivatives** and the latter in glacial acetic acid were oxidized with an excess of 30% hydrogen peroxide; during the latter step, as was observed previously,[2] deacetylation also occurred and the product obtained was 2- or 4-(trifluoromethyl)-phenothiazine-5,5-dioxide. These 5,5-dioxides, either because of their insolubility or lack of reactivity under the usual condensation conditions, gave low yields of the 10-3-dimethylaminopropyl derivatives.

In the ultraviolet, 10-dimethylaminopropyl-2-(trifluoromethyl)-phenothiazine hydrochloride showed two maxima at 255 and 305 mμ ($E^{1\%}_{1cm}$ 700, 90); four maxima, however, were shown by the corresponding 5-oxide, 235, 278, 302 and 348 mμ ($E^{1\%}_{1cm}$ 608, 256, 177, 116) and the corresponding N,5-dioxide 233, 274, 303 and 348 mμ ($E^{1\%}_{1cm}$ 548, 257, 173, 119); in the infrared, the latter two compounds showed deep bands at 9.8 μ, which is attributed to the S → O group.

The pertinent data on the oxygenated 10-dialkylaminoalkyl-(trifluoromethyl)-phenothiazines are summarized in Table IV.

Acknowledgment.—The microanalyses were carried out by Mr. Joseph F. Alicino and his associates. The infrared and ultraviolet spectra were determined by Dr. Nettie Coy and her associates.

Experimental Part

All melting and boiling point temperatures are uncorrected.

2- and 4-(Trifluoromethyl)-phenothiazines.—A mixture of 506 g. (2.14 moles) of 3-(trifluoromethyl)-diphenylamine, 134 g. (4.18 moles) of sulfur and 12.9 g. of iodine were fused at 150–160° for 3.5 hr. and the hot melt poured into 3.5 l. of warm toluene. The toluene solution was heated to boiling, treated with Hyflo and filtered hot. The filtrate was cooled to −5° and filtered to give 216 g. of 2-(trifluoromethyl)-phenothiazine, m.p. 183–185; concentration of the mother liquors by one-half and cooling gave an additional 45 g. of product. The over-all yield was 261 g. (45%). The filtrate from the second crop was freed of toluene and the residue distilled. The viscous distillate, b.p. 172–175° (0.5 mm.), solidified on cooling. It was recrystallized from ligroin to give 185 g. (32% yield) of 4-(trifluoromethyl)-phenothiazine, m.p. 72–73°.

Anal. Calcd. for $C_{13}H_8F_3NS$: C, 58.41; H, 3.01. Found: C, 58.84; H, 3.08.

10-(3-Dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine Hydrochloride.—The following description represents a typical preparation. A mixture of 26.7 g. (0.1 mole) of 2-(trifluoromethyl)-phenothiazine, 4.7 g. (0.12 mole) of sodamide, 14.6 g. (0.12 mole) of 3-dimethylaminopropyl chloride and 500 ml. of dry xylene was stirred and refluxed 17 hr. and the hot solution filtered. The filtrate

TABLE IV

OXYGENATED 10-DIALKYLAMINOALKYL-(TRIFLUOROMETHYL)-PHENOTHIAZINES AND THEIR DERIVATIVES

Side chain	Position of CF_3	Position of O	Mol. formula	Yield, %	M.p., °C.	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
$-(CH_2)_3N(CH_3)_2$	2	5	$C_{18}H_{19}F_3N_2OS \cdot C_2H_2O_4$[a,b]	85	213–215	52.39	4.62	6.11	52.78	4.57	6.15
$-(CH_2)_3N(CH_3)_2$	2	N,5	$C_{18}H_{19}F_3N_2O_2S \cdot 3H_2O$[c]	68	135–137	49.39	5.75	6.39	49.04	5.74	6.74
$-(CH_2)_3N(CH_3)_2$	4	5	$C_{18}H_{19}F_3N_2OS \cdot HCl \cdot H_2O$[d]	36	150–152 d.	51.11	5.24	6.62	51.32	5.08	6.43
$-(CH_2)_3N(C_2H_5)_2$	2	5	$C_{20}H_{23}F_3N_2OS \cdot C_2H_2O_4$[e,f]	36	229–230 d.			5.76			5 73
$-(CH_2)_3N(C_2H_5)_2$	2	N,5	$C_{20}H_{23}F_3N_2O_2S \cdot HCl$[g]	48	182–184 d.	53.50	5.17	6.24	53.79	4.99	6.21
$-(CH_2)_3N(CH_3)_2$	4	5,5	$C_{18}H_{19}F_3N_2O_2S \cdot HCl$[h,i]	5	240–241	51.36	4.79	6.65	51.68	4.68	6.72

[a] Recrystallized from 95% ethanol. [b] Free base, m.p. 99–100°. *Anal.* Calcd.: C, 58.68; H, 5.20. Found: C, 58.40; H, 5.25. Hydrochloride, m.p. 209–210°. *Anal.* Calcd.: C, 53.39; H, 4.98; N, 6.92. Found: C, 53.53; H, 5.06; N, 6.87. [c] Recrystallized from methyl ethyl ketone. [d] Recrystallized from isopropyl alcohol–ether. [e] Recrystallized from butanol. [f] Free base, m.p. 125–127°. *Anal.* Calcd.: C, 60.58; H, 5.85; N, 7.07. Found: C, 61.01; H, 5.73; N, 7.10. [g] Recrystallized from glacial acetic acid–ether. [h] Recrystallized from acetonitrile and ether. [i] Free base, m.p. 164–165°. *Anal.* Calcd.: C, 56.38; H, 4.99. Found: C, 56.57; H, 4.88.

was concentrated *in vacuo*, the residue was taken up in 400 ml. of ether and the ether solution was extracted with 200, 100 and 100 ml. of 5% hydrochloric acid. The hydrochloric acid extracts were washed with ether, made strongly alkaline with 40% aqueous sodium hydroxide and the **base** extracted with ether; the ether extracts were dried, concentrated and distilled to give 30 g. (85% yield) of product, b.p. 176° (0.7 mm.), $n^{23}D$ 1.5780.

The above distilled base in 300 ml. of dry ether was cooled and treated with a slight excess of ethereal HCl. The precipitated **hydrochloride** was filtered and dried; it weighed 34.0 g., m.p. 165–168° dec. A recrystallization from xylene gave 26.5 g. (69% yield) of product, m.p. 172–174° dec.

10-(3-Dimethylaminopropyl)-3-(trifluoromethyl)-phenothiazine Hydrochloride. 2-[2-Nitro-4-(trifluoromethyl)-phenylthio]-acetanilide.—A mixture of 23.7 g. (0.075 mole) of 2-[2-nitro-4-(trifluoromethyl)-phenylthio]-aniline, 35 ml. of acetic anhydride and 2.5 ml. of pyridine was heated on the steam-bath for 1.5 hr. and then concentrated *in vacuo* to a small volume. The product which crystallized on cooling was filtered, washed consecutively with water, 5% aqueous sodium bicarbonate and water and dried to give 24.9 g. (93% yield) of the **acetanilide**, m.p. 148–149°. An analytical sample, from isopropyl alcohol, melted at 148–149°.

Anal. Calcd. for $C_{15}H_{11}F_3N_2O_3S$: C, 50.55; H, 3.08. Found: C, 50.88; H, 3.11.

To a nitrogen diffused solution of 22 g. (0.33 mole) of 85% potassium hydroxide in 375 ml. of 95% ethanol was added 3.0 l. of acetone, the mixture was stirred and again diffused with nitrogen, 119.5 g. (0.33 mole of the **acetanilide** was added and the mixture distilled rapidly from the steam-bath. The residual material was treated with 1.8 l. of ether and 275 ml. of water, the ether layer was separated, washed with saturated sodium chloride solution, dried and concentrated. The **10-acetyl-3-(trifluoromethyl)-phenothiazine** was isolated as a viscous *gum*. This gum was dissolved in a mixture of 250 ml. of 95% ethanol and 50 ml. of concentrated hydrochloric acid and the solution refluxed for 2 hr. The cooled mixture was filtered to give 80 g. of **3-(trifluoromethyl)-phenothiazine**, m.p. 213–215° (lit.[5] m.p. 217–218°). The filtrate when concentrated to dryness gave 6 g. of additional material, m.p. 214–216°. The combined yield was 86 g. (96%). A mixture of 46.8 g. (0.175 mole) of 3-(trifluoromethyl)-phenothiazine, 125 ml. of acrylonitrile and 2 ml. of 40% Triton B was warmed to initiate reaction and then refluxed for 1 hr. The solution was concentrated to a small volume, cooled and the solid filtered. The crude product was recrystallized from acetone to give 34.7 g. (62% yield) of 3-(trifluoromethyl)-10-phenothiazinepropionitrile, m.p. 110–111°.[10]

Anal. Calcd. for $C_{16}H_{11}F_3N_2S$: N, 8.74. Found: N, 9.10.

To an ice-cooled slurry of 6.4 g. (0.17 mole) of lithium aluminum hydride in 500 ml. of anhydrous ether, with stirring, was added, in portions, 27.3 g. (0.085 mole) of 3-(trifluoromethyl)-10-phenothiazinepropionitrile. Subsequently, the mixture was refluxed and stirred for 1 hr., cooled and decomposed by the addition of 25 ml. of water and 10 ml. of 20% aqueous sodium hydroxide. The ether solution was separated, dried, concentrated and distilled to give 9.3 g. (33% yield) of **10-(3-aminopropyl)-3-(trifluoromethyl)-phenothiazine**. To the **3-aminopropyl derivative**, 9.2 g. (0.028 mole) in 14.7 g. (0.28 mole) of formic acid, was added 7 g. (0.086 mole) of 37% formalin and the mixture heated in an oil-bath at 90–100° for 8 hr. The mixture was cooled, filtered and the filtrate treated with 30.4 ml. of 0.955 *N* aqueous hydrochloric acid. The mixture was concentrated to dryness *in vacuo*, the residue was dissolved in 100 ml. of water and then made alkaline with an excess of 20% aqueous sodium hydroxide. **The base** was isolated, distilled and converted to the hydrochloride in the manner described above.

10-(4-Dimethylaminobutyl)-2-(trifluoromethyl)-phenothiazine Hydrochloride. 10-[4'-(2''-Tetrahydropyranoloxy)-1'-butyl]-2-(trifluoromethyl)-phenothiazine.—A mixture of 66.8 g. (0.25 mole) of 2-(trifluoromethyl)-phenothiazine, 11.7 g. (0.30 mole) of sodamide and 750 ml. of dry xylene were refluxed for 2 hr. The reaction mixture was cooled, and a solution of 58.6 g. (0.30 mole) of 2-tetrahydropyranyl-4-chlorobutyl ether[8] in 250 ml. of dry xylene was added dropwise. The mixture was then refluxed for 3.5 hr., filtered hot and the xylene removed *in vacuo*. The residue was extracted with 500 ml. of ether, the filtered ether extracts were concentrated and the residue distilled to give 97.8 g. (96% yield) of crude product, b.p. 200–202° (0.2 mm.). *Anal.* Calcd. for $C_{22}H_{24}F_3NOS$: C, 64.84; H, 5.93. Found: C, 62.44; H, 5.67. **10-(4-Hydroxybutyl)-2-(trifluoromethyl)-phenothiazine.**—A solution of 97.8 g. (0.24 mole) of the **pyranyl derivative**, 25 ml. of concentrated hydrochloric acid and 1 l. of 75% ethanol was refluxed for 1 hr. The alcohol was then distilled from the steam-bath and the residue extracted with ether. The dried ether extracts were concentrated and distilled to give 64.8 g. (79% yield) of product, b.p. 178–181° (0.3 mm.). *Anal.* Calcd. for $C_{17}H_{16}F_3NOS$: C, 60.10; H, 4.75. Found: C, 60.93; H, 4.93. **10-(4-Chlorobutyl)-2-(trifluoromethyl)-phenothiazine.** To a refluxing solution of 9.8 g. (0.03 mole) of 10-(4-hydroxybutyl)-2-(trifluoromethyl)-phenothiazine in 65 ml. of dry benzene was added dropwise 3.6 g. (0.03 mole) of thionyl chloride. The mixture was then refluxed for 1 hr. and poured into 50 ml. of ice-water. The mixture was treated with an excess of solid sodium bicarbonate, the organic layer was separated and the aqueous layer extracted with ether. The combined dried extracts were then concentrated and the residue distilled to give 6.6 g. of crude product, b.p. 182–185° (0.7 mm.), which was contaminated with some (2-trifluoromethyl)-phenothiazine. This crude distillate was dissolved in 25 ml. of boiling hexane and the solution cooled; the (2-trifluoromethyl)-phenothiazine was filtered off. Concentration of the filtrate gave 5.2 g. (48% yield) of crude product suitable for the next step.

Anal. Calcd. for $C_{17}H_{15}ClF_3NS$: Cl, 9.90. Found: Cl, 7.69.

10-(4-Dimethylaminobutyl)-2-(trifluoromethyl)-phenothiazine Hydrochloride.—A solution of 5.0 g. of crude 10-(4-chlorobutyl)-2-(trifluoromethyl)-phenothiazine in 10 ml. of anhydrous dimethylamine was kept in a sealed tube for seven days at room temperature. The tube was opened, the excess dimethylamine allowed to evaporate and the pasty residue dissolved in 50 ml. of 10% hydrochloric acid. This

(10) This cyanoethylation procedure has been used by Smith, ref. 7, in the reaction between 2-(trifluoromethyl)-phenothiazine and acrylonitrile.

acid solution was extracted with three 50-ml. portions of ether, treated with an excess of 20% potassium hydroxide and the liberated base extracted with ether. Concentration of the ether extracts gave 4.2 g. (82% yield) of **base** as a viscous oil. The oil, in ether, was converted to the hydrochloride in the usual manner.

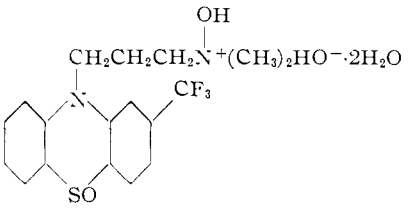
10-(3-Diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine 5-Oxide. 10-(3-Diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine Oxalate.—To 11.4 g. (0.03 mole) of 10-(3-diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine in 100 ml. of 95% ethanol was added a solution of 2.7 g. (0.03 mole) of anhydrous oxalic acid in 10 ml. of 95% ethanol; the oxalate separated directly and was filtered to give 14.1 g. (100% yield) of product, m.p. 192–194° dec., unchanged by recrystallization from water. This product, in a mixture of 250 ml. of 95% ethanol and 100 ml. of water, was treated with 3.4 ml. of 30% hydrogen peroxide and the solution refluxed for 17 hr. The mixture was concentrated *in vacuo* to give a quantitative yield of the **oxalate of the 5-oxide**, m.p. 229–230° dec. The m.p. was unaffected by a recrystallization from *n*-butyl alcohol. This latter product was decomposed with warm 10% aqueous sodium hydroxide and the **base** extracted with chloroform. The chloroform extracts were concentrated to dryness and the crystalline residue recrystallized from Skellysolve E to give **10-(3-diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine 5-oxide.**

10-(3-Diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine N,5-Dioxide Hydrochloride.—A solution of 11.4 g. (0.03 mole) of 10-(3-diethylaminopropyl)-2-(trifluoromethyl)-phenothiazine, 100 ml. of 95% ethanol and 6.8 ml. of 30% hydrogen peroxide was refluxed for 17 hr. and then concentrated to dryness. The residual oil crystallized. The crude **base** could be recrystallized from ethyl acetate or methyl ethyl ketone–hexane and formed colorless crystals, m.p. 136–138° dec. On standing, however, the crystals changed to a deep yellow color; satisfactory analytical data could not be obtained. The crude base was dissolved in 200 ml. of boiling methyl ethyl ketone, the solution was cooled and treated with an excess of ethereal HCl; the salt which separated was filtered and recrystallized from a mixture of glacial acetic acid–dry ether to give the product.

10-(3-Dimethylaminopropyl)-4-(trifluoromethyl)-phenothiazine 5,5-Dioxide Hydrochloride.—A mixture of 40 g. (0.15 mole) of 4-(trifluoromethyl)-phenothiazine 75 ml. of acetic anhydride and 4 ml. of pyridine was refluxed for 4 hr. and then concentrated to dryness. The residual solid was washed with hexane to give 45.9 g. (quantitative yield) of crude 10-acetyl-4-(trifluoromethyl)-phenothiazine, m.p. 135–137°. An analytical sample was recrystallized from isopropyl alcohol and melted at 140–141°. *Anal.* Calcd. for $C_{15}H_{10}F_3NOS$: C, 58.24; H, 3.23. Found: C, 57.81; H, 3.27. **The acetyl derivative**, 30.3 g. (0.098 mole), 33.3 g. of 30% hydrogen peroxide, 225 ml. of glacial acetic acid and 25 ml. of acetic anhydride were refluxed for 4 hr. and the mixture cooled. The solid which separated was filtered; it weighed 19.7 g., m.p. 273–274°. A recrystallization from aqueous Cellosolve raised the m.p. to 275–276°. As noted previously, deacetylation had occurred during the oxidation so that the product obtained was **4-(trifluoromethyl)-phenothiazine 5,5-dioxide.** The yield was 68%. *Anal.* Calcd. for $C_{13}H_8F_3NO_2S$: C, 52.17; H, 2.69. Found: C, 52.06; H, 2.86. The condensation between 14.1 g. (0.047 mole) of 4-(trifluoromethyl)-phenothiazine 5,5-dioxide, 0.1 mole of 3-dimethylaminopropyl chloride and 2.7 g. (0.07 mole) of sodamide in 250 ml. of xylene was carried out under the usual conditions. The reaction mixture was filtered hot and the filtrate concentrated to dryness. The residue, 1.7 g., m.p. 159–160°, was recrystallized from toluene to give 1.4 g. (8% yield) of **10-(3-dimethylaminopropyl)-4-(trifluoromethyl)-phenothiazine 5,5-dioxide**, m.p. 164–165°. To 1.3 g. of the **5,5-dioxide** in 25 ml. of warm toluene was added slowly with stirring a slight excess of ethereal hydrogen chloride. The solid which separated, m.p. 233–235°, was recrystallized from acetonitrile–ether to give 1 g. (70% yield) of **10-(3-dimethylaminopropyl)-4-(trifluoromethyl)-phenothiazine 5,5-dioxide hydrochloride**, m.p. 240–241°.

10-(3-Dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine 5-Oxide, Hydrochloride.—To a solution of 9.7 g. (0.036 mole) of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine in 25 ml. of acetonitrile was added 3.28 g. (0.036 mole) of oxalic acid in 10 ml. of acetonitrile. **The oxalate** separated directly and was filtered; the crude product, m.p. 193–195° dec., was recrystallized from acetonitrile to give 6 g. (49% yield) of pure product, m.p. 196–197° dec. A solution of 6 g. of the **oxalate**, 150 ml. of absolute ethanol and 1.6 g. of 30% hydrogen peroxide when refluxed for only 1 hr. began to deposit a crystalline product; after 5 hr. of refluxing, heating was interrupted and the mixture was cooled and filtered to give 5.5 g. (88% yield) of the **oxalate of the 5-oxide derivative**, m.p. 213–215° dec.; a recrystallization from 95% ethanol did not affect the m.p. The oxalate was decomposed with warm 5% aqueous sodium hydroxide, the liberated base extracted with ether, the ether solution was dried and treated with an excess of ethereal hydrogen chloride. The hydrochloride which separated was filtered and recrystallized from chlorobenzene to give 2.5 g. (55% yield) of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine 5-oxide hydrochloride, m.p. 203–205°.

10-(3-Dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine N,5-Dioxide Trihydrate.—A mixture of 15.4 g. (0.044 mole) of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine, 150 ml. of 95% ethanol and 10 ml. of 30% hydrogen peroxide was refluxed for 24 hr. and concentrated on the steam-bath. The residual oil crystallized partially when kept in the cold. A wash with 50 ml. of dry ether removed the oily by-product and left behind a nicely crystalline material. After recrystallization from methyl ethyl ketone, the product sintered at 80° and melted with decomposition at 135–137°. An analytical sample when pistol-dried at 58° lost considerable weight; the dried sample thus obtained was very hygroscopic in air, forming a trihydrate. Since the product is 2% soluble in water at room temperature, it is suggested that the hydrated compound probably has the structure



2-(Trifluoromethyl)-phenothiazine 5,5-Dioxide.—A mixture of 13.4 g. (0.05 mole) of 2-(trifluoromethyl)-phenothiazine, 25 ml. of acetyl chloride and 50 ml. of acetic anhydride was refluxed for 4 hr. and then concentrated *in vacuo* on the steam-bath. To the viscous residue was added 50 ml. of glacial acetic acid and 17 ml. of 30% hydrogen peroxide. The mixture was gradually heated to the boiling point at which temperature a vigorous exothermic reaction occurred. The source of heat was removed until the reaction subsided after which the mixture was refluxed for 4 hr. During this time a crystalline solid began to separate. The mixture was cooled and filtered to give 13.5 g. (90% yield) of product, m.p. 265–267°. On recrystallization from 95% ethanol, the product melted at 268–270°. Again, deacetylation has occurred during the oxidation.

Anal. Calcd. for $C_{13}H_8F_3NO_2S$: C, 52.19; H, 2.70. Found: C, 52.22; H, 2.87.

NEW BRUNSWICK, N. J.