[Contribution from the Squibb Institute for Medical Research]

# 4-{3-[10-(2-Trifluoromethyl)-phenothiazinyl]-propyl}-1-piperazine-ethanol[1] and Related Compounds. II[2]

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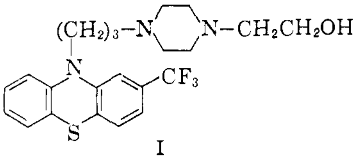
A series of 2-(trifluoromethyl)-phenothiazines carrying a 4-substituted-1-piperazinylpropyl side chain in the 10-position are described. The 4-substituents include H–, $CH_3$–, $HOCH_2CH_2$–, $HOCH_2CH_2OCH_2CH_2$–, $CH_2{:}CHOCH_2CH_2$–, $(CH_3O)_2CHCH_2$–, $C_2H_5O_2CCH_2$– and $C_2H_5O_2C$–. In addition, two related derivatives of 7-nitro-2-(trifluoromethyl)-phenothiazine, the corresponding substituents being $CH_3$– and $HOCH_2CH_2$–, are also reported.

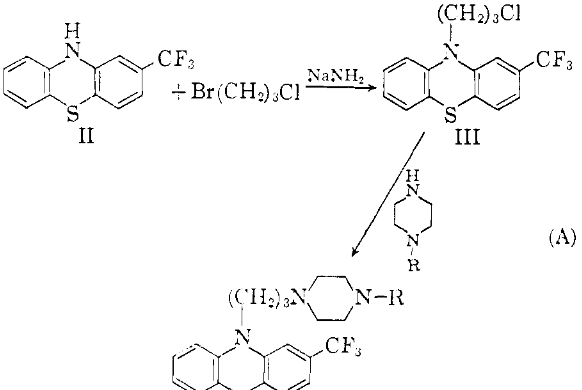
In a previous publication,[2] we described the preparation of 10-(3-dimethylaminopropyl)-2-(trifluoromethyl)-phenothiazine and related compounds. As an extension of this program, we have synthesized a series of 2-(trifluoromethyl)-phenothiazines which carry a 4-substituted-1-piperazinylpropyl side chain in the 10-position. One of these compounds, 4-{3-[2-(trifluoromethyl)-10-phenothiazinyl]-propyl}-1-piperazine-ethanol (I) has been



I

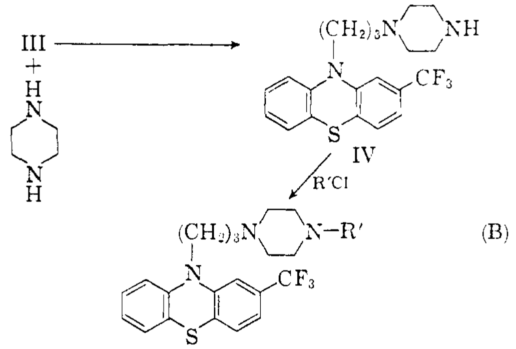
found to be a highly potent and useful ataractic agent for chronic hospitalized psychotic patients.[3] The clinical applications of another compound in this series have been summarized by Brill.[4]

The two synthetic procedures used to obtain these compounds are outlined in equations A and B.



IV, R = H V, R = $CH_3$
VI, R = $CO_2C_2H_5$

The reaction of II with trimethylene chlorobromide has been studied in some detail since III was a precursor for many of the desired final compounds. Solvent, temperature, heating time and molar ratio of reactants were varied, but despite this, crude III always contained 15–20% of unreacted II.



XII, R′ = $CH_2CO_2C_2H_5$
XIII, R′ = $CH_2CH(OCH_3)_2$
XIV, R′ = $CH_2CH_2OCH{:}CH_2$
XV, R′ = $CH_2CH_2OCH_2CH_2OH$

The separation of II from III was difficult. Distillation, *in vacuo*, of the mixture was found to be impractical due to concomitant decomposition as well as co-distillation (or sublimation) of II; III[5] could be separated from II by fractional crystallization from petroleum ether, but this procedure involved loss of material. Fortunately, for large scale preparative procedures, the crude mixture of II and III could be used directly in the next step with piperazine or a 1-substituted piperazine, since the tertiary nitrogen base then obtained was readily separated from non-basic contaminants.

The reaction of III with anhydrous piperazine gave IV as the principal product, but led, also, to the formation of 1,4- bis-3-{10-[2-(trifluoromethyl)-phenothiazinyl]-propyl}-piperazine (VII); VII was found, also, in the non-volatile pot residues from the distillation of I, prepared according to equation A. It is visualized that VII was formed in the latter case according to the equation I + III → VII.

The reactions of IV with β-chloroethyl vinyl ether, β-chloroethyl β-hydroxyethyl ether, chloroacetaldehyde dimethyl acetal and ethyl chloroacetate proceeded satisfactorily and gave the expected products. The reaction of IV with β-chloroethyl carbamate, however, did not give the carbamate of I. Instead, the product VIII isolated as the dimaleate, possessed the same empirical formula as the dimaleate of I, yet melting points and mixture melting points made it abundantly clear that these derivatives were different. In the infrared, the spectra of the dihydrochlorides of I and VIII were similar, except in the 10–12 μ

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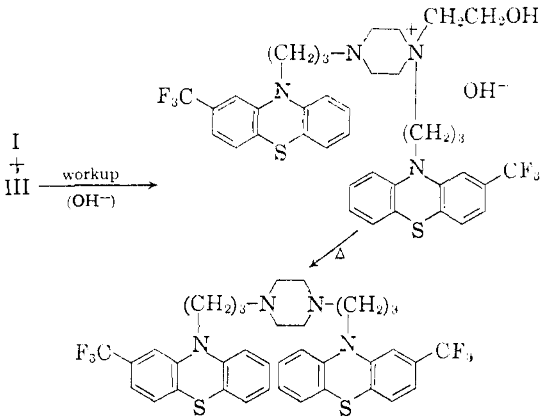
[1] The E. R. Squibb & Sons trademark for this product is Prolixin.

[2] For Paper I, see H. L. Yale, F. Sowinski and J. Bernstein, This Journal, **79**, 4375 (1957).

[3] H. F. Darling, "Diseases of the Nervous System," in press.

[4] H. Brill, "Trifluoperazine—Clinical and Pharmacological Aspects," Lea and Febiger, Philadelphia, Pa., 1958.

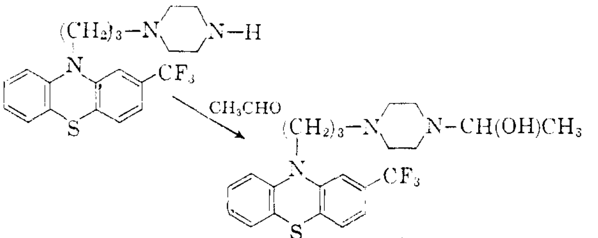
[5] While III is the predominant product, there is evidence that some 10-(3-bromopropyl)-2-(trifluoromethyl)-phenothiazine is also formed in this reaction; see the Experimental part for details.



VII

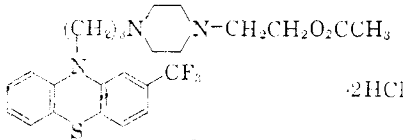
region, where variations in the side chain would be expected to alter the spectra. The absorption band at 3 $\mu$ in VIII confirmed the presence of a hydroxyl group.

The product from the reaction of IV with acetaldehyde gave a dimaleate identical with the dimaleate of VIII, and this established the structure of VIII[6]



VIII

Acetyl chloride and I in chloroform solution gave the *acetate* of I (IX).



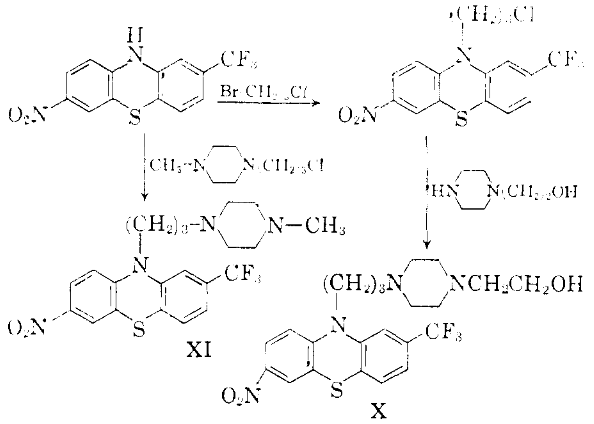
IX

The dioxalate of I, with one equivalent of hydrogen peroxide in ethanol[2] gave the 5-oxide.

We are reporting, also, the synthesis of 4-{3-[10-(7-nitro-2-trifluoromethyl)-phenothiazinyl]-propyl}-1-piperazineëthanol (X) and 10-[3-(4-methyl-1-piperazine)-propyl]-7-nitro-2-(trifluoromethyl)-phenothiazine (XI). The synthetic procedures employed are indicated in the equation.

## Experimental Part

All melting and boiling points are uncorrected. The authors are indebted to Dr. Nettie Coy and Miss Barbara Keeler for the infrared spectra. The microanalyses were carried out by Mr. J. F. Alicino and his associates.



The physical properties and analyses for the compounds described below will be found in Table I or in the Experimental Part.

**4-{3-[2-(Trifluoromethyl)-10-phenothiazinyl]propyl}-1-piperazine-ethanol (I).**—A mixture of 200 g. (0.75 mole) of 2-(trifluoromethyl)-phenothiazine (II), 157.5 g. (1.0 mole) of trimethylene chlorobromide, 35 g. (0.9 mole) of sodium amide and 3.0 l. of dry toluene was stirred and refluxed for about 18 hours, filtered hot and the filtrate concentrated *in vacuo* on the steam-bath. The residual oil, which consists of a mixture of II and III (see below for details on their separation), 195 g. (1.5 moles) of 1-piperazine-ethanol, 112.5 g. (0.75 mole) of sodium iodide and 1500 ml. of methyl ethyl ketone were stirred and refluxed for 18 hours, concentrated on the steam-bath and the residue poured into a mixture of 225 ml. of concentrated hydrochloric acid, 1775 ml. of water and 600 ml. of ether. The mixture was shaken thoroughly, the acid layer was separated [from the ether layer there was recovered 30 g. (15%) of unreacted II], cooled and made alkaline with 40% aqueous potassium hydroxide solution. The alkaline mixture was saturated with potassium carbonate and then extracted with three 600-ml. portions of ether. The ether extracts were washed with saturated sodium chloride solution, dried, concentrated from the steam-bath and the residual oil distilled to give 144.4 g. (34% yield) of **4-{3-[2-(trifluoromethyl-10-phenothiazinyl]-propyl}-1-piperazine-ethanol**. Some decomposition occurred during the distillation. A solution of the **base** in 1500 ml. of anhydrous ether was cooled in ice-water and treated dropwise with a solution of 25 g. of hydrogen chloride in 1 l. of anhydrous ether. The crude **dihydrochloride** which separated was filtered, dried and recrystallized from absolute ethanol to give 105.3 g. (63% yield) of pure dihydrochloride.

**4-{3-[2-(Trifluoromethyl)-10-phenothiazinyl]-propyl}-1-piperazine-ethanol Dimaleate (Ia).**—To the base (8.7 g., 0.02 mole) dissolved in 200 ml. of hot acetonitrile was added a solution of 4.65 g. (0.04 mole) of maleic acid in 100 ml. of hot acetonitrile, the solutions were mixed thoroughly and allowed to cool. The solid which separated was filtered and recrystallized from methyl ethyl ketone to give 11.3 g. of the dimaleate.

Compounds IV and V were prepared in a similar manner, using anhydrous piperazine and 1-methylpiperazine, respectively, in place of 1-piperazine-ethanol. The preparation of VI is described below.

**Ethyl 4-{3-[2-(Trifluoromethyl)-10-phenothiazinyl]-propyl}-1-piperazinecarboxylate Oxalate (VI).**—A mixture of 15.0 g. (0.044 mole) of 10-(3-chloropropyl)-2-(trifluoromethyl)-phenothiazine and 20.7 g. (0.13 mole) of 1-carbethoxypiperazine was kept for 7 days at room temperature and the semi-crystalline mass partitioned between 250 ml. of 0.8 $N$ hydrochloric acid and 250 ml. of ether. The acid layer was separated, washed with two 250-ml. portions of ether, cooled and treated with an excess of 20% aqueous sodium hydroxide solution. The liberated oil was extracted with ether, the ether solution was dried, concentrated and the residue distilled to give 7 g. (34% yield) of **base**. The **base**, 2.5 g., in 10 ml. of acetonitrile and 1.17 g. of oxalic acid in 10 ml. of acetonitrile was mixed and the solution diluted with anhydrous ether to the point of incipient crystallization. When the mixture was cooled, the **oxalate** crystallized; the crystals were filtered to give 2.7 g. of crude prod-

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(6) No reactions or indications of stability of $\beta$-chloroethyl carbamate are to be found in the literature. Since identical products were obtained from IV with either $\beta$-chloroethyl carbamate or acetaldehyde, it is assumed that under the alkaline experimental conditions, dehydrochlorination of $\beta$-chloroethyl carbamate to vinyl carbamate occurred and that the latter compound hydrolyzed to acetaldehyde.

Although aldehyde–amine adducts are often unstable, piperazine forms stable adducts with aldehydes (formaldehyde). Thus, piperazinemethanols are stable to aqueous hydrochloric acid and aqueous sodium hydroxide [British Patent 752,331, July 11, 1956; *C. A.*, **51**, 9717*d* (1957)].

TABLE I

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

| | | | | | | | | | | | | Salts | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Carbon, % | | Hydrogen, % | | Nitrogen, % | | | | | Carbon, % | | Hydrogen, % | | Nitrogen, % | |
| Cpd. | R in RN N(CH$_2$)$_3$ | Mol. formula | Yield, % | Boiling point °C. | Mm. | Calcd. | Found | Calcd. | Found | Calcd. | Found | Mol. formula | Yield, % | M.p., °C. | Calcd. | Found | Calcd. | Found | Calcd. | Found |
| I | HOCH$_2$CH$_2$ | $C_{22}H_{26}F_3N_3OS$ | 34 | 250–252 | 0.3 | 60.39 | 60.34 | 5.99 | 5.93 | ... | ... | $C_{22}H_{26}F_3N_3OS\cdot 2HCl^c$ | 63 | 231–233 | 51.76 | 51.73 | 5.52 | 5.86 | 8.23 | 8.00 |
| | | | | | | | | | | | | $C_{22}H_{26}F_3N_3OS\cdot 2C_4H_4O_4{}^f$ | 84 | 165–166 | 53.81 | 53.81 | 5.12 | 4.93 | 6.28 | 6.14 |
| | | | | | | | | | | | | $C_{22}H_{26}F_3N_3OS\cdot 2C_2H_2O_4{}^e$ | 100 | 220–221 d. | 50.56 | 50.96 | 4.90 | 5.15 | .. | .. |
| IV | H | $C_{20}H_{22}F_3N_3S$ | 27 | 208–210 | .08 | 61.04 | 60.97 | 5.63 | 5.49 | 10.68 | 10.40 | $C_{20}H_{22}F_3N_3S\cdot 2HCl\cdot 2H_2O^b$ | 72 | 232–234 | 47.82 | 48.30 | 5.23 | 5.32 | 8.37 | 8.50 |
| V | CH$_3$ | $C_{21}H_{24}F_3N_3S$ | 78 | 214–216 | .2 | 61.89 | 61.97 | 5.91 | 5.73 | ... | ... | $C_{21}H_{24}F_3N_3S\cdot 2HCl^c$ | 60 | 242–243 | ... | .. | .. | .. | 8.74$^d$ | 8.71 |
| | | | | | | | | | | | | $C_{21}H_{24}F_3N_3S\cdot 2C_4H_4O_4{}^e$ | 89 | 194–195 | 54.45 | 54.90 | 5.04 | 4.86 | 6.57 | 6.46 |
| VI | C$_2$H$_5$O$_2$C | $C_{23}H_{26}F_3N_3O_2S$ | 14 | 230–240 | .25 | 59.33 | 60.20 | 5.63 | 5.69 | ... | ... | $C_{23}H_{26}F_3N_3O_2S\cdot C_2H_2O_4{}^c$ | 57 | 174–175 | 54.04$^i$ | 54.46 | 5.07 | 5.23 | 7.56 | 7.63 |
| VIII | CH$_3$CH(OH) | $C_{22}H_{26}F_3N_3OS$ | $^a$ | ..... | .. | ... | ... | .. | .. | ... | ... | $C_{22}H_{26}F_3N_3OS\cdot 2HCl^c$ | | 205–208 | 51.76 | 51.95 | 5.52 | 5.78 | 8.23 | 8.21 |
| | | | | | | | | | | | | $C_{22}H_{26}F_3N_3OS\cdot 2C_4H_4O_4{}^h$ | 10 | 210–212 | 53.81 | 54.09 | 5.12 | 5.53 | 6.68 | 6.51 |
| IX | CH$_3$CO$_2$CH$_2$CH$_2$ | $C_{24}H_{28}F_3N_3O_2S$ | .. | ..... | .. | ... | ... | .. | .. | ... | ... | $C_{24}H_{28}F_3N_3O_2S\cdot 2HCl^g$ | 77 | 233–235 | 52.17 | 52.07 | 5.46 | 5.46 | 7.60 | 7.77 |
| XII | C$_2$H$_5$O$_2$CCH$_2$ | $C_{24}H_{28}F_3N_3O_2S$ | $^a$ | ..... | .. | ... | ... | .. | .. | ... | ... | $C_{24}H_{28}F_3N_3O_2S\cdot 2C_4H_4O_4{}^k$ | 34 | 165–167 | 54.00 | 54.77 | 5.10 | 4.91 | 5.90 | 5.96 |
| XIII | (CH$_3$O)$_2$CHCH$_2$ | $C_{24}H_{30}F_3N_3O_2S$ | $^a$ | .... | .. | ... | ... | .. | .. | ... | ... | $C_{24}H_{30}F_3N_3O_2S\cdot C_4H_4O_4{}^k$ | 10 | 210–212 | ...$^l$ | ... | .. | .. | 7.03 | 7.16 |
| XIV | CH$_2$=CHOCH$_2$CH$_2$ | $C_{24}H_{28}F_3N_3OS$ | 54 | 242–245 | 0.5 | ... | ... | .. | .. | 9.07 | 9.26 | $C_{24}H_{28}F_3N_3OS\cdot 2C_4H_4O_4{}^f$ | 39 | 165–167 | ... | ... | .. | .. | 6.04 | 6.45 |
| XV | HOCH$_2$CH$_2$OCH$_2$CH$_2$ | $C_{24}H_{30}F_3N_3O_2S$ | $^a$ | ..... | .. | ... | ... | .. | .. | ... | ... | $C_{24}H_{30}F_3N_3O_2S\cdot 2C_4H_4O_4{}^g$ | 49 | 155–157 | 53.85 | 54.08 | 5.37 | 5.64 | 5.89 | 5.82 |

[a] The undistilled base was converted to the dimaleate. [b] Recrystallized from acetonitrile containing 2–3% of water. [c] Recrystallized from absolute ethanol. [d] *Anal.* Calcd.: Cl, 14.76. Found: Cl, 14.66. [e] Recrystallized from 95% ethanol; previously reported by P. N. Craig, E. A. Nodiff, J. J. Lafferty and G. E. Ullyot, *J. Org. Chem.*, **22**, 709 (1957). [f] Recrystallized from methyl ethyl ketone. [g] Recrystallized from isopropyl alcohol. [h] Recrystallized from water. [i] *Anal.* Calcd.: neut. equiv. (HClO$_4$), 555. Found: neut. equiv., 567. [j] *Anal.* Calcd.: S, 4.61. Found: S, 4.86. [k] Recrystallized from acetonitrile. [l] *Anal.* Calcd.: S, 5.37; neut. equiv. (HClO$_4$), 299. Found: S, 5.29; neut. equiv., 302.

uct. Recrystallization first from absolute ethanol and then from water gave 1.7 g. (57% yield) of the pure product.

**Separation of 2-(Trifluoromethyl)-phenothiazine (II) from 10-(3-Chloropropyl)-2-(trifluoromethyl)-phenothiazine (III).**—The mixture of II and III, obtained from an experiment identical with the one described above for the preparation of I, was dissolved in 600 ml. of boiling petroleum ether (b.p. 115–125°). The solution was allowed to cool spontaneously to room temperature and the crystals of II filtered. The filtrate was concentrated to one-half volume on the steam-bath, *in vacuo*, allowed to cool, and filtered to give an additional amount of II. The total recovery of II was 32 g. (16%). The petroleum ether filtrate was now concentrated to dryness and the residual oil kept at room temperature. During several weeks, the oil partially crystallized. The crystals were filtered with suction and purified by repeated recrystallization from pentane to give 77 g. (32% yield) of a pale yellow crystalline product, m.p. 70–71°. Analysis indicated that this material contained *ca.* 1% of bromine, presumably present as the **10-(3-bromopropyl) derivative.**

*Anal.* Calcd. for $C_{16}H_{13}F_3ClNS$: N, 4.07; Cl, 10.32; S, 9.32. Found: N, 4.24; Cl, 10.63; S, 9.74.

**1,4-Bis-3-{10-[2-(trifluoromethyl)-phenothiazinyl]-propyl}-piperazine (VII) (A).**—The non-volatile residue from the distillation of I (obtained from a reaction of 2 kg. of II) was dissolved in about 500 ml. of acetone. The dark solution on standing for several weeks at room temperature deposited an orange colored crystalline product. This was filtered and weighed 74 g., m.p. 168–170°. Two recrystallizations from *n*-butyl alcohol gave the pure product, m.p. 173–175°.

*Anal.* Calcd. for $C_{36}H_{34}F_6N_4S_2$: C, 61.70; H, 4.89; N, 8.00. Found: C, 61.96; H, 4.89; N, 7.92.

When VII was dissolved in boiling ethanolic hydrogen chloride and the solution cooled, the **dihydrochloride** separated, m.p. softens 132°, dec. 140°. A recrystallization from absolute ethanol did not change the m.p. The dihydrochloride was insoluble in water.

*Anal.* Calcd. for $C_{36}H_{34}F_6N_4S_2\cdot 2HCl$: Cl, 9.16. Found: Cl, 9.16.

Hot solutions of 0.7 g. (0.001 mole) of VII in 10 ml. of absolute ethanol and 0.23 g. (0.002 mole) of maleic acid in 5 ml. of absolute ethanol were mixed and cooled. The gelatinous product which separated was filtered and recrystallized from acetonitrile to give the **dimaleate**, m.p. 167–168°.

*Anal.* Calcd. for $C_{36}H_{34}F_6N_4S_2\cdot 2C_4H_4O_4$: C, 56.62; H, 4.54; N, 5.98. Found: C, 56.90; H, 4.43; N, 6.01.

(B).—The non-volatile residue from the distillation of the **base IV** (obtained from a reaction of 100 g. of II) crystallized on cooling. It was washed with acetone to give 3 g. of yellow crystals. Two recrystallizations from *n*-butyl alcohol gave the pure product, m.p. 173–175°. A mixture m.p. with the product from (A) was 173–175°.

**4-{3-[2-(Trifluoromethyl)-10-phenothiazinyl]-propyl}-1-piperazineëthyl Acetate Dihydrochloride (IX).**—To a solution of 7.0 g. (0.016 mole) of I in 50 ml. of anhydrous chloroform was added dropwise, with stirring and ice-cooling, a solution of 1.4 g. (0.018 mole) of acetyl chloride in 10 ml. of anhydrous chloroform. The mixture was concentrated to about half-volume and diluted with an equal volume of methyl ethyl ketone. The crystalline product was filtered to give 7.2 g. of crude product, m.p. 233–235° dec. A recrystallization from isopropyl alcohol gave 6.8 g. (77% yield) of pure **dihydrochloride.**

**10-{3-[4-(Vinyloxyethyl)-piperazinyl]-propyl}-2-(trifluoromethyl)-phenothiazine Dimaleate (XIV).**—A mixture of 21.2 g. (0.054 mole) of IV, 7.4 g. (0.05 mole) of anhydrous potassium carbonate, 11 g. of $\beta$-chloroethyl vinyl ether and 50 ml. of anhydrous toluene was stirred and refluxed for 18 hours, cooled, diluted with two volumes of anhydrous ether and filtered. The filtrate was washed with water, the toluene–ether solution was dried, concentrated and the residue distilled to give 13.5 g. (54% yield) of **base**, b.p. 242–245° (0.5 mm.). **The base**, 13.5 g., in 50 ml. of warm acetonitrile was added to a warm solution of 6.7 g. of maleic acid in 50 ml. of acetonitrile. The crystalline product which separated was filtered and melted at 147–149°. One recrystallization from methyl ethyl ketone raised the m.p. to 162–164° dec.; a second recrystallization from the same solvent gave the pure product, m.p. 165–167°. The yield was 8 g. (39%).

Compounds XII, XIII and XV were similarly prepared by substituting ethyl chloroacetate, chloroacetaldehyde dimethyl acetal and β-chloroethyl β-hydroxyethyl ether, respectively, for the β-chloroethyl vinyl ether in the above synthesis.

**α-Methyl-4-{3-[2-(trifluoromethyl)-10-phenothiazinyl]-propyl}-piperazinemethanol Dimaleate (VIII) (A).**—A mixture of 19.8 g. (0.05 mole) of IV, 12.4 g. (0.1 mole) of β-chloroethyl carbamate, 6.9 g. (0.05 mole) of anhydrous potassium carbonate and 100 ml. of anhydrous toluene was stirred and refluxed for 18 hours, filtered, and the filtrate concentrated to dryness on the steam-bath *in vacuo*. To the residual oil in 250 ml. of warm acetonitrile was added a solution of 13.4 g. of maleic acid in 150 ml. of warm acetonitrile. The mixture was warmed for 0.5 hr., cooled and the solid filtered. It weighed 5 g. A recrystallization from water gave 3.5 g. (10% yield) of product, m.p. 210–212° dec. A mixture m.p. with Ia was 160–200°.

The above dimaleate was dissolved in a minimum amount of warm water and the base liberated with an excess of 20% aqueous potassium hydroxide solution. The base was extracted into ether, the ether solution was washed with water and dried. The filtered ether solution was cooled and treated with a slight excess of ethereal hydrogen chloride. The very hygroscopic salt which separated was filtered and recrystallized from absolute ethanol to give the pure dihydrochloride; m.p. 205–208°.

(B).—A mixture of 3.9 g. (0.01 mole) of IV, 1.32 g. (0.03 mole) of acetaldehyde and 100 ml. of anhydrous toluene sealed in a Carius tube was heated 18 hours at 93°. The tube was cooled, opened and the toluene solution concentrated *in vacuo* to give a black tar. This was extracted with 50 ml. of boiling acetonitrile, and the acetonitrile solution decanted from the insoluble material. To the acetonitrile solution was added a solution of 2.32 g. (0.02 mole) of maleic acid in 20 ml. of warm acetonitrile. The dark tan solid which separated on cooling was filtered and washed with a little acetonitrile. The solid weighed 1.0 g., m.p. 188–190°. Recrystallization first from 95% ethanol and then from water gave 0.3 g. of material, m.p. 210–212° dec. A mixture m.p. with VIIIa was 210–212° dec., and the infrared spectra of the two compounds were identical.

*Anal.* Calcd. for $C_{22}H_{26}F_3N_3OS{\cdot}2C_4H_4O_4$: N, 6.28; S, 4.79. Found: N, 6.56 S, 4.97.

**4-{3-[2-(Trifluoromethyl)-10-phenothiazinyl]-propyl}-piperazine-ethanol 5-Oxide Hydrochloride.**—Four and one-half grams (0.01 mole) of I in 200 ml. of 95% ethanol and a solution of 1.8 g. of oxalic acid in 50 ml. of 95% ethanol were mixed rapidly. Subsequently, the mixture was heated under reflux for 0.5 hr., cooled, and the dioxalate filtered. It was an extremely insoluble compound, m.p. 215–217° dec. One recrystallization from 95% ethanol raised the m.p. to 220–221° dec. This dioxalate, 250 ml. of 95% ethanol, 100 ml. of water and 1.3 g. of 30% hydrogen peroxide were refluxed for 24 hours, then concentrated *in vacuo* on the steam-bath. The residual yellow gum was dissolved in water, and the solution treated with an excess of 10% aqueous sodium hydroxide solution. The liberated base was insoluble in ether but could be extracted with chloroform. The chloroform extracts were dried and concentrated. The residual oil was dissolved in 10 ml. of isopropyl alcohol and the solution treated with ethereal hydrogen chloride. The crystalline solid which separated was filtered and recrystallized from chlorobenzene to give 2 g. (40% yield) of product, m.p. 213–215°.

*Anal.* Calcd. for $C_{22}H_{26}F_3N_3O_2S{\cdot}HCl$: C, 53.92; H, 5.56; N, 8.58; Cl, 7.24; S, 6.54. Found: C, 53.85; H, 5.46; N, 8.43; Cl, 7.28; S, 6.71.

**4-{3-[10-(7-Nitro-2-trifluoromethyl)-phenothiazinyl]-propyl}-1-piperazine-ethanol Dimaleate (X).**—A mixture of 31.2 g. (0.1 mole) of 7-nitro-2-(trifluoromethyl)-phenothiazine, 4.3 g. (0.11 mole) of sodium amide and 300 ml. of diethylene glycol dimethyl ether was heated to 90° and 18.9 g. of trimethylene chlorobromide added dropwise. The mixture was then stirred and heated for 18 hours at 145°, cooled and to it was added 22.5 g. of sodium iodide and 26 g. of 1-piperazine-ethanol. Subsequently, the reaction was allowed to proceed for 18 hours at 115°, the mixture diluted with 300 ml. of anhydrous xylene and filtered. The filtrate was concentrated on the steam-bath *in vacuo*, and the residue, in acetonitrile, converted to the maleic acid salt. The crude salt was twice recrystallized from 95% ethanol to give 12 g. (17% yield) of pure product, m.p. 185–187° dec.

*Anal.* Calcd. for $C_{22}H_{25}F_3N_4O_3S{\cdot}2C_4H_4O_4$: C, 50.42; H, 4.65; N, 7.84. Found: C, 50.41; H, 4.85; N, 7.61.

**10-[3-(4-Methyl-1-piperazinyl)-propyl]-7-nitro-2-(trifluoromethyl)-phenothiazine (XI).**—A mixture of 31.2 g. (0.1 mole) of 7-nitro-2-(trifluoromethyl)-phenothiazine, 4.3 g. (0.11 mole) of sodium amide and 300 ml. of diethylene glycol dimethyl ether was heated to 90° and treated dropwise with 21.2 g. of 4-methyl-1-piperazinepropyl chloride. The mixture was then heated to 135° and maintained for four hours at this temperature, cooled, and filtered. The filtrate was concentrated on the steam-bath *in vacuo*. When the residual oil was treated with acetonitrile, crystallization occurred. The solid was filtered to give 31 g. of crude product, m.p. 124–126°. After one recrystallization from hexane, there was obtained 23 g. (51% yield) of pure product, m.p. 127–128°.

*Anal.* Calcd. for $C_{21}H_{23}F_3N_4O_2S$: C, 55.73; H, 5.12; N, 12.38. Found: C, 55.99; H, 5.00; N, 12.04.

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[CONTRIBUTION FROM THE SQUIBB INSTITUTE FOR MEDICAL RESEARCH]

# 6-(Trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide and Related Compounds

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The synthesis of 6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (II) and its 3-methyl- (XIII) and 3-ethyl- (XV) derivatives, 3,4-dihydro-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (V) and its ethyl derivative (VI), as well as 3-oxo-6-(trifluoromethyl)-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide (XXIII) is described. Both II and V have demonstrated clinical usefulness as diuretic agents. The effect on the diuretic activity of these compounds caused by the replacement of a benzene by a pyridine nucleus has also been ascertained by synthesizing 1,2,4-pyrido[2,3-e]thiadiazine-7-sulfonamide-1,1-dioxide (XVIII), 3,4-dihydro-1,2,4-pyrido[2,3-e]thiadiazine-7-sulfonamide-1,1-dioxide (XIX) and 6-methyl-1,2,4-pyrido[2,3-e]thiadiazine-7-sulfonamide-1,1-dioxide (XX). Elucidation of the structures of the acetyl and propionyl derivatives of 5-amino-α,α,α-trifluoro-2,4-toluenedisulfonamide (I), precursors, respectively, of XIII and XV, has involved to a considerable extent a study of the infrared spectra of these derivatives. These data are presented and discussed.

The clinical effectiveness of 6-chloro-1,2,4-benzothiadiazine-7-sulfonamide-1,1-dioxide[1a] as a diuretic agent[1b,c] suggested to us the synthesis of the corresponding 6-(trifluoromethyl) derivative. This reasoning was based on the observation that the

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[1] (a) F. C. Novello and J. M. Sprague, THIS JOURNAL, **79**, 2028 (1957); (b) R. V. Ford and C. L. Spurr, *Southern Soc. Clin. Research Meeting*, **1**, 26 (1957), through *Am. J. Med.*, **22**, 965 (1957); (c) R. V. Ford, J. H. Moyer and C. L. Spurr, *A.M.A. Arch. of Int. Med.*, **100**, 582 (1957).