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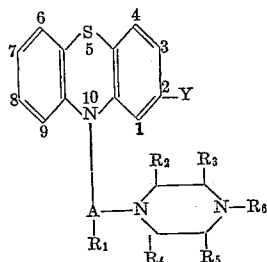
3,058,979 NEW PERFLUOROALKYLPHENOTHIAZINE DERIVATIVES

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This invention relates to new 10-(piperazinylalkyl)-per-
fluoroalkylphenothiazine derivatives. The novel com-
pounds of this invention are of value as therapeutic
agents.

More specifically, the compounds of this invention have
utility as antiemetics, tranquilizers, antihistaminics, spas-
molytics, antishock agents and potentiators of various
drugs such as analgetics and anesthetics. When used as
tranquilizers, these compounds have the ability to abate
mental disturbances such as anxiety, confusion or excita-
tion without physical incapacitation. In addition, these
compounds have chemotherapeutic or anti-microbial
activity, such as antibacterial and fungicidal activity.
Further, the novel compounds of this invention have a
surprisingly low degree of toxicity.

The compounds of this invention are 10-(piperazinyl-
alkyl) - perfluoroalkylphenothiazine derivatives rep-
resented by the general formula:



when:

Y represents perfluoroalkyl of 1 to 3 carbon atoms,
preferably $-\text{CF}_3$.

A represents a straight or branched alkylene chain of
from 2 to 6 carbon atoms separating the nitrogen atoms
linked thereto by at least two carbon atoms,

R_1 is H or OH bonded to an internal methylene group
in A, that is, not bonded to a carbon attached to a nitro-
gen,

R_2, R_3, R_4 and R_5 each represent methyl, ethyl or
hydrogen,

R_6 represents the following:

Hydrogen,

Alkyl, for example, methyl, ethyl, butyl hexyl, cyclo-
pentyl and cyclohexyl,

Alicyclicalkyl of from 6 to 10 carbon atoms, such as
 β -cyclohexylethyl and β -cyclopentylmethyl,

Alkenyl of from 2 to 6 carbon atoms such as allyl and
isocrotonyl,

Dialkylamino-lower-alkyl preferably dimethyl or diethyl-
amino-lower-alkyl, for example, dimethylaminobutyl
and diethylaminoethyl,

Hydroxy-lower-alkyl, for example, hydroxyethyl and
hydroxybutyl,

Hydroxy-lower-alkyl-oxy-lower-alkyl, for example, ω -hy-
droxyethoxyethyl and ω -hydroxypropoxypropyl,

Monocyclic aralkyl, for example, phenyl-lower-alkyl, such
as benzyl, cinnamyl, phenethyl and ω -phenylbutyl,

Acyl such as aliphatic acyl of from 1 to 6, preferably
1 to 4 carbon atoms, for example, formyl, acetyl,
butyryl, propionyl, caproyl, isocaproyl, or crotonoyl
or equivalently halogenated derivatives of said aliphatic
aclys such as chloroacetyl, trifluoroacetyl, hepta-

2

fluorobutyryl and dichloroacetyl; alicyclic aliphatic
acyl of from 7 to 10 carbon atoms, such as cyclo-
pentylpropionyl, hexahydrobenzoyl and cyclohexyl-
butyryl; monocyclic aryl-aliphatic acyl of from 6 to
10 carbons, such as cinnamoyl, phenylacetyl, phenyl-
propionyl or 2-furaneacrylyl; monocyclic aroyl such
as furoyl or benzoyl; lower carbalkoxy, such as carbo-
methoxy or carboethoxy; carbobenzoxy; carbamyl and
N-substituted carbamyl, for example, dialkyl carbamyl
such as diethylcarbamyl or dimethylcarbamyl and N-
phenyl carbamyl,

Acyloxy-lower-alkyl, for example, aliphatic acyloxy-
lower-alkyl having from 1 to 6, preferably from 2
to 4 carbon atoms in the acyloxy portion, such as,
acetoxyethyl, crotonoxyethyl, butyryloxybutyl or
isocaproxyethyl and monocyclic aroyloxy-lower-
alkyl such as benzoyloxy-lower-alkyl. Any of the acyl
moieties defined above under "acyl" can be used as sub-
stituents on the oxygen atom of the hydroxy-lower-
alkyl moieties.

Advantageous compounds of this invention are rep-
resented by the above structural formula when:

Y represents trifluoromethyl,

A represents ethylene, propylene or 2-methylpropylene,
 R_2, R_3, R_4 and R_5 represent hydrogen,
 R_6 represents hydrogen, alkyl of from 1 to 4 carbon atoms,

hydroxy-lower-alkyl of from 2 to 4 carbon atoms or ali-
phatic acyloxy-lower-alkyl having 1 to 4 carbon atoms
in the acyloxy portion and 2 to 4 carbon atoms in the
alkyl portion.

By the term "alkyl" where used herein, aliphatic groups
having not more than 6 carbon atoms and, preferably
not more than 4 carbon atoms, is intended except where
otherwise specifically indicated.

The term "lower alkyl" is used in connection with
alkylene residues and as thus used represents aliphatic
groups of from 2 to 6 carbon atoms, preferably 2 to 4
carbon atoms except where otherwise specifically in-
dicated.

It is also implied, as one skilled in the art will recog-
nize, that when R_1 is hydroxy, it is not attached to the
end members of the alkylene chain.

This invention also includes salts of the above defined
bases formed with non-toxic organic and inorganic acids.
Such salts are easily prepared by methods known to
the art. The base is reacted with either the calculated
amount of organic or inorganic acid in aqueous miscible
solvent, such as acetone or ethanol, with isolation of the
salt by concentration and cooling, or an excess of the
acid in aqueous immiscible solvent, such as ethyl ether
or chloroform, with the desired salt separating directly.
Exemplary of such organic salts are those with maleic,
fumaric, benzoic, ascorbic, pamoic, succinic, bismethyl-
enesalicylic, methanesulfonic, ethanedisulfonic, acetic,
propionic, tartaric, salicylic, citric, gluconic, lactic, malic,
mandelic, cinnamic, citraconic, aspartic, stearic, palmitic,
itaconic, glycolic, p-aminobenzoic, glutamic, benzene sul-
fonic and theophylline acetic acids as well as the 8-
halotheophyllines, for example, 8-chlorotheophylline and
8-bromotheophylline. Exemplary of such inorganic salts
are those with hydrochloric, hydrobromic, sulfuric, sul-
famic, phosphoric and nitric acids. Of course, these salts
may also be prepared by the classical method of double
decomposition of appropriate salts which is well-known
to the art.

The compounds of this invention are prepared using
2-perfluoroalkylphenothiazine starting materials which are
prepared by methods well-known to the art and most
readily by classical methods of phenothiazine forma-
tion, such as thionation of properly substituted 2-perfluoro-

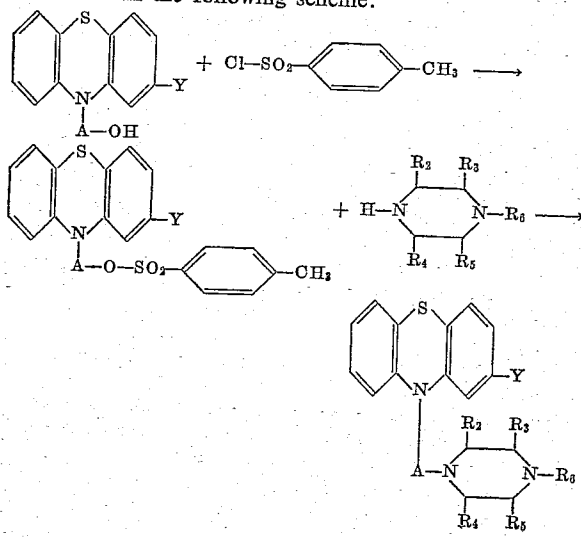
roalkyldiphenyl amines, namely, the Bernthsen reaction. Reference may be had to "S. P. Massie, Chemical Reviews, 54; 797 (1954)."

The 2-perfluoroalkylphenothiazine nucleus is condensed with a reactive piperazinyllalkyl ester having the desired piperazinyllalkyl group. The condensation is carried out by refluxing the reactants in an inert aromatic solvent, such as benzene, xylene or toluene, in which at least one of the reactants must be soluble. A suitable acid-binding agent may be included, such as an alkali metal amide, preferably sodium amide or potassium amide; an alkali metal hydroxide, preferably potassium hydroxide; an alkali metal hydride, preferably sodium hydride; or alkali metal aryl or alkyl compounds, preferably phenyl sodium.

The piperazinyllalkyl ester is preferably used as the free base although the acid addition salts may be used with a corresponding increase in the amount of inorganic base as defined above. Any reactive piperazinyllalkyl ester containing the desired substituted piperazinyllalkyl group may be used, such as the halides, preferably bromide or chloride, or the sulfonic or sulfuric ester, preferably the p-toluene sulfonate.

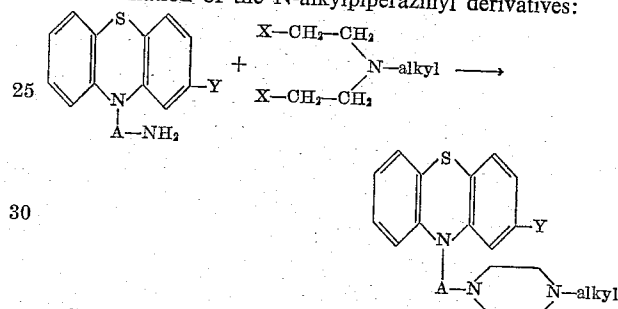
The 10-(piperazinyllalkyl)-perfluoroalkylphenothiazines are alternatively prepared by methods which involve chemical modifications of an alkyl chain which has a reactive, terminal group such as a halogen, a carboxy, tosylate, aldehyde or cyano group and which is attached to the 10-position of the parent 2-perfluoroalkylphenothiazine. While such methods are conveniently used to prepare 10-(N-substituted-piperazinyllalkyl)-2-perfluoroalkylphenothiazine, they are particularly valuable for the preparation of the piperazines unsubstituted at the terminal N position, such as 10-(ω-piperazinyllalkyl)-2-perfluoroalkylphenothiazine or 10-[ω-(2',5'-diethylpiperazinyl)-alkyl]-2-perfluoroalkylphenothiazine. These synthetic procedures will be more evident from the following description.

For example, the 2-perfluoroalkylphenothiazines substituted in the 10-position with an alkyl chain containing a terminal reactive ester group, such as tosylate, are prepared as in the following procedure. A 2-tetrahydropyranyll ether of a haloalkanol is condensed in an inert solvent, such as xylene, with a 2-perfluoroalkylphenothiazine in the presence of an acid binder, such as sodamide, to give a 10-(ω-tetrahydropyranyloxyalkyl)-2-perfluoroalkylphenothiazine. The protective pyranil group is removed with acid, for example, hydrochloric acid. The resulting 10-(ω-hydroxyalkyl)-2-perfluoroalkylphenothiazine derivative is then esterified with an appropriate acyl halide, such as tosyl (p-toluene sulfonyl) chloride to give the desired reactive ester, in this case the tosylate. The resulting ester is reacted with a piperazine, preferably at reflux in alcohol with a mild alkali. This procedure is illustrated in the following scheme:



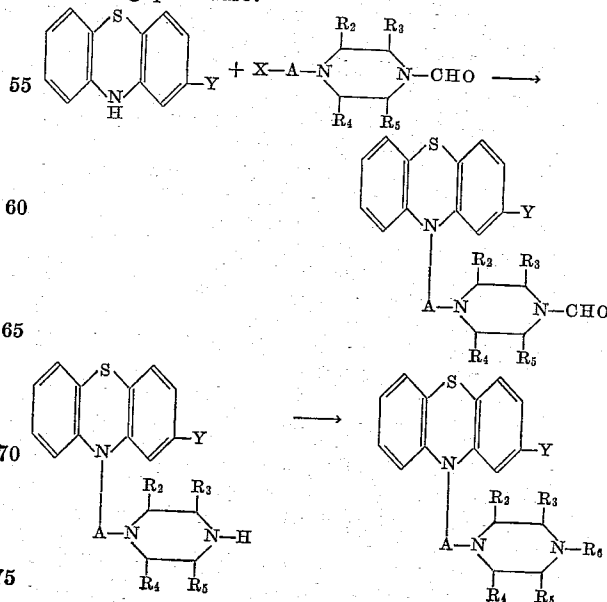
It is, at times, convenient to react the 10-(ω-hydroxyalkyl)-perfluoroalkylphenothiazine derivative obtained as hereabove described with a reactive inorganic halide, such as thionyl chloride, thionyl bromide or phosphorous pentachloride, in a non-ionic solvent, such as benzene or xylene, to give a 10-(ω-haloalkyl)-perfluoroalkylphenothiazine which is then reacted with a piperazine preferably in excess or in the presence of an acid binder, such as sodium carbonate in an aqueous alcohol medium.

As a further example of the preparation of these compounds, certain 10-(ω-piperazinyllalkyl)-2-perfluoroalkylphenothiazine derivatives are prepared from the terminal primary amine derivatives by condensing a 10-(ω-aminoalkyl)-2-perfluoroalkylphenothiazine (made readily by reduction of the ω-cyanoalkyl analogue) with a substituted bis-(β-haloalkyl)-amine, such as an alkylbis-(β-haloalkyl)-amine, to give a 10-[ω-(N-substituted-piperazinyllalkyl)-perfluoroalkylphenothiazine such as a 10-[ω-(N-alkylpiperazinyl)-alkyl]-perfluoroalkylphenothiazine as specifically illustrated in the following scheme showing the formation of the N-alkylpiperazinyl derivatives:



X as used in the above and following scheme equals halogen.

Easily removed groups may be substituted for the N-alkyl radical, such as where R₆ is acyl, in order to obtain the compounds of this invention in which R₆ is H by this method. This is the best synthetic route for the preparation of the compounds where R₆ is H which compounds are particularly important as intermediates to prepare analogues with other R₆ substituents by reaction with reactive esters such as bromides, iodides or chlorides or with ethylene oxide. This route of synthesis conveniently gives compounds of this invention in good yield and purity which would be obtained otherwise with more difficulty. For example, the production of 10-(ω-piperazinyllalkyl)-2-perfluoroalkylphenothiazines may be accomplished by protecting the nitrogen of the piperazinyllalkyl ester with a formyl group by the following procedure:



5

The monosubstituted piperazine is heated at reflux with an excess of a formic acid ester, such as methyl or ethyl formate. The volatiles are removed in vacuo and the desired N-formylpiperazinylalkyl ester isolated by distillation or fractional crystallization. Optionally, the N-formylpiperazinylalkyl ester may be formed by reversing the order of reaction, for instance by N-formylating ω -hydroxy-lower-alkylpiperazine and then reacting with thionyl chloride to form N-(ω -chloro-lower-alkyl)-N-formylpiperazine. This N-formyl ester is reacted with 2-perfluoroalkylphenothiazine to give 10-[ω -(N-formylpiperazinyl)-alkyl]-2-perfluoroalkylphenothiazine. The protective formyl group is removed by mild hydrolysis conditions, such as with dilute sodium hydroxide solution, to give the desired 10-(ω -piperazinylalkyl)-2-perfluoroalkylphenothiazine. However, when a benzyl group is used, it cannot be removed by hydrolysis but will be removed by catalytic hydrogenation.

This compound is further N-substituted by alkylation methods, such as with a reactive ester as discussed above in the presence of base, for instance with a substituted alkyl halide with sodium amide or potassium carbonate. Alternatively, the alkylation can be accomplished by reductive methods, for example, with formaldehyde-formic acid mixture, by reaction with an oxide such as ethylene oxide, or by N-acylation followed by reduction of the resulting amide, for instance N-acetylation followed by reduction with lithium aluminum hydride in tetrahydrofuran.

The foregoing is a general description of the main synthetic routes in the preparation of 10-(ω -piperazinylalkyl)-2-perfluoroalkylphenothiazine derivatives. It will be readily apparent to one skilled in the art that variations of these procedures are possible. Of particular advantage as preparative procedures are the first two methods discussed, namely, alkylation of 2-perfluoroalkylphenothiazine in the 10-position of the nucleus by a reactive dialkylaminoalkyl ester and utilization of 2-perfluoroalkylphenothiazine derivatives substituted in the 10-position with aliphatic chains containing a reactive terminal group.

It will be readily apparent to one skilled in the art that certain of the compounds of this invention, notably those in which A is represented by an aliphatic carbon chain branched so that an asymmetric carbon atom is formed or where the ω -piperazinyl moiety is C-substituted, may be present as optical or cis-trans isomers. The connotation of the general formulae presented herein is to include the separated d. or l. optical isomers as well as the dl. mixture of these isomers. If desired, the isomers may be separated for individual use by separation methods known to the art, such as fractional crystallization of the d-tartrate salts of the perfluoroalkylphenothiazine derivatives. Alternatively, a synthesis starting with an optically active side chain may yield the desired optical isomer.

The following examples will be illustrative of compounds of this invention and the procedures for their preparation and will serve to make fully apparent all of the compounds embraced by the general formula given above and the preparation thereof respectively.

EXAMPLE I

A mixture of 17.2 g. of 2-trifluoromethylphenothiazine, 3.1 g. of sodamide and 14 g. of 1-(3'-chloropropyl)-4-methylpiperazine in 200 ml. of xylene is heated at reflux with stirring for two hours. The salts are extracted into 150 ml. of water. The xylene layer is then extracted with several portions of dilute hydrochloric acid. The acid extracts are combined and neutralized with ammonium hydroxide solution. The products, 10-[3'-(4'-methyl-1''-piperazinyl)-propyl]-2-trifluoromethylphenothiazine, is taken into benzene and purified by vacuum distillation, B.P. 202 to 210° C. at 0.6 mm.

Four grams of the basic oil are treated with 2.2 g. of

6

maleic acid in ethyl acetate. Cooling the concentrated solution caused the separation of crystals of 10-[3'-(4'-methyl-1''-piperazinyl)-propyl]-2-trifluoromethylphenothiazine dimaleate; M.P. 185° C. (dec.).

EXAMPLE II

A suspension of 69.0 g. of 2-trifluoromethylphenothiazine in 1 l. of toluene with 10.9 g. of sodium amide is heated at reflux with high speed stirring for 15 minutes. A solution of 54.1 g. of 1-formyl-4-(3'-chloropropyl)-piperazine, [prepared by formylating 1-(3'-hydroxypropyl)-piperazine by refluxing in an excess of methyl formate, purifying the 1-formyl-4-(3'-hydroxypropyl)-piperazine by vacuum distillation, reacting this compound with an excess of thionyl chloride at reflux and isolating the desired 1-formyl-4-(3'-chloropropyl)-piperazine by neutralization with sodium carbonate solution followed by distillation] in 200 ml. of toluene is added. The reflux period is continued for four hours. The cooled reaction mixture is treated with 200 ml. of water. The organic layer is extracted twice with dilute hydrochloric acid. The acid extracts are made basic with ammonia and extracted with benzene. The volatiles are taken off in vacuo at the steam bath to leave a dark brown oil which is 10-[3'-(N-formylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine. It can be distilled at 260° C. at 10 microns, or used directly without distillation if desired.

EXAMPLE III

A solution of 103.5 g. of 10-[3'-(N-formylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine (made as in Example II) in 400 ml. of ethanol and 218 ml. of water containing 26 ml. of 40% sodium hydroxide solution is heated at reflux for two hours. The alcohol is taken off in vacuo on the steam bath. The residue is swirled with benzene and water. The dried benzene layer is evaporated in vacuo. The residue is vacuum distilled to give a viscous, yellow oil, 10-(3'-piperazinylpropyl)-2-trifluoromethylphenothiazine, distilling at 210-235° C. at 0.5 to 0.6 mm.

This material, 3.9 g., is dissolved in ethyl acetate and reacted with 2.4 g. of maleic acid. Concentration and cooling gives the crystalline dimaleate which, after drying at 100° C. in an Abderhalden pistol, melts at 140-142° C. as the hemihydrate salt.

EXAMPLE IV

A suspension of 14.0 g. of 10-(3'-piperazinylpropyl)-2-trifluoromethylphenothiazine (made as in Example III), 6.4 g. of β -bromoethyl acetate and 2.6 g. of potassium carbonate in 100 ml. of toluene is stirred at reflux for 16 hours. Water (50 ml.) is added to the cooled mixture. The organic layer is extracted into dilute hydrochloric acid. After neutralizing the extracts and taking the separated base up in benzene, a viscous, yellow residue is obtained by evaporating the organic solvent in vacuo. This oil is chromatographed on alumina. The purified fraction of 7.7 g. of 10-[3'-(N-acetoxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine is taken up in ethyl acetate and mixed with 25 ml. of alcoholic hydrogen chloride. Concentration in vacuo separates white crystals of the dihydrochloride salt, M.P. 225-227° C.

EXAMPLE V

A solution of 33 g. of 10-(2'-chloroethyl)-2-trifluoromethylphenothiazine (prepared by the reaction of ethylene oxide with 2-trifluoromethylphenothiazine followed by subsequent treatment of the β -hydroxyethyl compound with thionyl chloride) and 25 g. of anhydrous piperazine in 200 ml. of isoamyl alcohol is heated at reflux for twelve hours. The reaction mixture is then washed well with water. The organic layer is extracted with dilute hydrochloric acid. After neutralizing with ammonia and extracting with ethyl acetate, drying and evaporating the acetate extracts gives 5 g. of the crude base, 10-(2'-piper-

azinyloethyl)-2-trifluoromethylphenothiazine. After molecular distillation of the residue, the dimaleate is prepared in ethyl acetate solution following the procedure of Example I.

Three grams of the base is heated at reflux in aqueous methanol with one equivalent of ethyl p-toluenesulfonate with sodium carbonate for ten hours. The strongly basic residue after evaporation is extracted with ether. The dried ether extracts are combined and treated with gaseous hydrogen chloride to give crude 10-[2'-(4''-ethyl-1''-piperazinyl)-ethyl]-2-trifluoromethylphenothiazine dihydrochloride, M.P. 210–215° C. (dec.).

The acid fumarate salt of this base is prepared by combining 4.2 g. of the base with 2.6 g. of fumaric acid in ethanol and adding ether to cloudiness. The mixture is then cooled in a Dry Ice/isopropanol bath to separate the desired difumarate salt.

EXAMPLE VI

A mixture of 10 g. of 10-(2'-piperazinylethyl)-2-trifluoromethylphenothiazine (prepared as in Example V) in 50 ml. of 85% formic acid solution is warmed to 50° C. and 15 ml. of 37% formalin solution is added over a 15 minute period. The reaction mixture is held at 50 to 60° C. until the evolution of carbon monoxide ceases. The mixture is neutralized with dilute sodium hydroxide solution to give an insoluble oil. This base is extracted into benzene and vacuum distilled to give 10-[2'-(4''-methyl-1''-piperazinyl)-ethyl]-2-trifluoromethylphenothiazine as a clear oil, B.P. 205 to 210° C. at 0.5 mm.

A solution of 500 mg. of the base in ethyl acetate is saturated with dry hydrogen chloride gas. Trituration with ether separates crystals of the dihydrochloride salt, M.P. 253° C.

EXAMPLE VII

A solution of 1.0 g. of 10-[3'-(N-acetoxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine (made as in Example IV) in 25 ml. of 1 N hydrochloric acid is heated at reflux briefly. Neutralization with dilute sodium carbonate solution and extraction with benzene gives the oily base, 10-[3'-(N-β-hydroxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine. The base is reacted with an excess of an alcoholic hydrogen chloride solution. Trituration with ether separates crystals of the dihydrochloride salt, M.P. 224°–226° C.

EXAMPLE VIII

Sixteen grams of 10-(2'-cyanoethyl)-2-trifluoromethylphenothiazine (prepared by reacting 2-trifluoromethylphenothiazine with acrylonitrile under alkaline conditions) is suspended in 500 ml. of dry ethyl ether. A solution of 8 g. of lithium aluminum hydride in 250 ml. of ether is slowly added. The reaction mixture is then heated at reflux with stirring for 24 hours. The complex is carefully destroyed by the addition of methanol. After filtration, the filtrate is evaporated in vacuo. The residue is extracted with several 50 ml. portions of 10% hydrochloric acid. The combined acid extracts are neutralized with concentrated ammonium hydroxide solution. The separated base is taken into dry ether and treated with gaseous hydrogen chloride to give 10-(3'-aminopropyl)-2-trifluoromethylphenothiazine hydrochloride.

A solution of 32.5 g. of 10-(3'-aminopropyl)-2-trifluoromethylphenothiazine, 21 g. of butyl bis-(β-chloroethyl)-amine in 300 ml. of butanol is heated at reflux for eight hours. Tributylamine (40 ml.) is added to the mixture and the reflux period is extended for eight hours. The volume of the reaction mixture is reduced on the steam bath at the water pump. After dilution of the residue with water, the base is extracted into chloroform. The dried chloroform extracts are concentrated. The basic residue is fractionally distilled to give an oily base, 10-[3'-(4''-butyl-1''-piperazinyl)-propyl]-2-trifluoromethylphenothiazine, B.P. 202 to 207° C. at 0.05 mm.

A solution of 800 mg. of the base in 25 ml. of ethyl acetate-ethanol is treated with 500 mg. of citric acid in ethanol. Concentration and cooling separates the dicitrate salt.

EXAMPLE IX

A solution of 5.4 g. of 2-trifluoromethylphenothiazine, 1.0 g. of sodium amide and 4.2 g. of 3-chloro-1-(N,2',5'-trimethylpiperazinyl)-propane in 100 ml. of toluene is heated at reflux for four hours. After working up as in Example I, 10-[3'-(N,2'',5''-trimethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine is obtained by molecular distillation at 200° C. at 10 microns.

A warm solution of 2.5 g. of this base in 50 ml. of ethyl acetate is titrated with a saturated solution of salicylic acid in ethyl acetate. The salicylate salt is separated by concentration and cooling.

EXAMPLE X

A suspension of 3.9 g. of 10-(3'-piperazinylpropyl)-2-trifluoromethylphenothiazine (made as in Example III), 2.0 g. of 2-bromo-1-diethylaminoethane and 0.5 g. of sodium amide in 50 ml. of benzene is heated at reflux with stirring for six hours. The reaction mixture is isolated by the procedure of Example I. The crude syrup, 10-[3'-(β-N-diethylaminoethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine, is purified by molecular distillation, at 195° C. at 1 micron.

EXAMPLE XI

A mixture of 18 g. of the 10-(3'-chloro-2'-methylpropyl)-2-trifluoromethylphenothiazine (prepared by the condensation of 1-bromo-3-chloro-2-methylpropane with 2-trifluoromethylphenothiazine) and 25 g. of N-methylpiperazine in 100 ml. of methanol is heated at reflux for three days. The volatiles are removed in vacuo on the steam bath. The residue is shaken with sodium hydroxide pellets and washed with 100 ml. portions of water, then extracted with benzene. The dried and washed organic extracts are evaporated at the water pump to give crude 10-[2'-methyl-3'-(4''-methyl-1''-piperazinyl)-propyl]-2-trifluoromethylphenothiazine which is purified by forming the dihydrochloride salt by reacting the base with ethereal hydrogen chloride in ethyl acetate and then recrystallizing the resulting salt from ethanol/ether. The dihydrochloride salt melts at either 167–168° C., or 185–186° C., depending on which polymorphic form is prepared.

EXAMPLE XII

A solution of 24.0 g. of 10-(3'-hydroxypropyl)-2-trifluoromethylphenothiazine p-toluene sulfonate (prepared by reacting 2-trifluoromethylphenothiazine with γ-bromopropyltetrahydropyranyl ether, removing the protective group with mineral acid and acylating with tosyl chloride in pyridine), 20.0 g. of N-hydroxyethoxyethylpiperazine in 300 ml. of ethanol with 10.0 g. of potassium carbonate is heated for six hours with stirring. The solution is diluted with water, evaporated in vacuo and extracted with ethyl acetate. The dried organic extract is evaporated to leave a crude syrup of 10-[3'-(N-hydroxyethoxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine.

EXAMPLE XIII

A solution of 13.4 g. of 2-trifluoromethylphenothiazine, 12.0 g. of N-ω-chlorohexyl-N-methylpiperazine and 2.0 g. of sodamide in 250 ml. of xylene is heated at reflux for 40 hours. After working up the reaction mixture by the procedure of Example I, a crude syrup, 10-[6'-(N-methylpiperazinyl)-hexyl]-2-trifluoromethylphenothiazine, is isolated.

A solution of 2.0 g. of this base dissolved in ether is saturated with dry hydrogen bromide gas to separate crystals of the dihydrobromide salt.

EXAMPLE XIV

Heptafluoropropylbenzene (180 g.) is slowly added to a mixture of nitric acid (d. 1.5) and concentrated sulfuric acid while maintaining the temperature at 20–30° C. The reaction mixture is quenched in an ice slurry, taken up in benzene and dried. Distillation at 100° C. at 10 mm. gives 1-heptafluoropropyl-3-nitrobenzene. A mixture of 125 g. of this compound in 300 ml. of purified dioxane is reduced at 2,000 p.s.i. with 15 g. of Raney nickel catalyst. Dilution with benzene, filtering the catalyst and evaporation gives a residue, 3-heptafluoropropylaniline, B.P. 95 to 96° C. at 12 mm.

Equivalent amounts of potassium carbonate, 2-chlorobenzoic acid and the aniline with 5.0 g. of copper powder in 500 ml. of amyl alcohol are heated at reflux with stirring for 24 hours. The basic reaction mixture is subjected to steam distillation. The residue is an aqueous slurry of the desired product as the sodium salt, 2-(3'-heptafluoropropylphenylamino)-benzoic acid. The free acid is obtained by trituration with excess dilute hydrochloric acid.

The water-washed aminobenzoic acid (225 g.) is decarboxylated by heating at 200° C. until the evolution of carbon dioxide ceases. A mixture of 33.5 g. of the resulting crude solid, 3-heptafluoropropyldiphenylamine, and 17.4 g. of sulfur and 0.3 g. of iodine is heated at 160–180° C. until the evolution of hydrogen sulfide ceases. The reaction mass is then extracted with hot benzene. Concentration and cooling separates greenish yellow platelets of 2-heptafluoropropylphenothiazine.

A suspension of 20.0 g. of 2-heptafluoropropylphenothiazine, 10.0 g. of 3-chloro-1-(N-methylpiperazinyl)propane and 1.5 g. of lithium amide in 300 ml. of toluene is heated at reflux for four hours. After working up the mixture as in Example I, a viscous syrup, 2-heptafluoropropyl - 10 - [3' - (N - methylpiperazinyl) - propyl] - phenothiazine, is obtained by molecular distillation at 205° C. and 15 microns.

A solution of 2.0 g. of this base in 25 ml. of ethyl acetate is reacted with a slight excess of maleic acid in ethyl acetate. Concentration and cooling gives the dimaleate salt.

EXAMPLE XV

A suspension of 3.9 g. of 10-(3'-piperazinylpropyl)-2-trifluoromethylphenothiazine (made as in Example III), 2.3 g. of n-hexyl iodide and 4.0 g. of potassium carbonate in 75 ml. of xylene is heated at reflux with stirring for eight hours. The reaction mixture is filtered. The filtrate is washed with water, dried and concentrated. The residue is weighed, taken up in ethyl acetate and treated with two equivalents of maleic acid to give crude 10 - [3' - (N - hexylpiperazinyl) - propyl] - 3 - trifluoromethylphenothiazine dimaleate, which is recrystallized from ethanol.

EXAMPLE XVI

A suspension of 7.8 g. of 10-(3'-piperazinylpropyl)-2-trifluoromethylphenothiazine (made as in Example III), 3.4 g. of ω -bromobutanol and 8.0 g. of potassium carbonate in 150 ml. of xylene is heated at reflux with stirring for five hours. After working up the reaction mixture as in Example XV, and distilling the crude basic residue, a viscous syrup is obtained, 10-[3'-(N- ω -hydroxybutylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine.

A solution of 1.1 g. of the base is dissolved in 25 ml. of pyridine and 0.5 ml. of butyryl chloride is added. After standing at room temperature for 12 hours, the reaction mixture is quenched. The separated product is washed well with water, dried in vacuo and taken up in ethyl acetate ether. Dry hydrogen chloride gas is passed through the solution to separate crystals of 10-[3'-(N- ω -butyryloxybutylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine dihydrochloride.

EXAMPLE XVII

A solution of 3.9 g. of 10-(3'-piperazinylpropyl)-2-trifluoromethylphenothiazine (made as in Example III), in 150 g. of benzene is swirled while 1.8 g. of phenylacetyl chloride is added dropwise. After standing overnight, the separated crystals of 10-[3'-(N-phenylacetyl-piperazinyl) - propyl]-2-trifluoromethylphenothiazine hydrochloride are removed by filtration and washed with ether.

EXAMPLE XVIII

A solution of 3.8 g. of 10-(2'-piperazinylethyl)-2-trifluoromethylphenothiazine (made as in Example V) in 150 g. of benzene with 4 ml. of pyridine is swirled while 3 ml. of acetic anhydride are added. The reaction mixture is allowed to stand overnight and evaporated to dryness. The residue after the usual acid extraction and neutralization is taken up in ethyl acetate and reacted with one equivalent of maleic acid to give 10-[2'-(N - acetyl-piperazinyl) - ethyl] - 2 - trifluoromethylphenothiazine maleate.

EXAMPLE XIX

A solution of 8.6 g. of 10-[3'-(N-hydroxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine (made as in Example VII) in 50 g. of pyridine is swirled as 3.0 g. of benzoyl chloride is added. The reaction mixture, after standing for eight hours, is poured into a large volume of water. The material which separates is washed well with water, taken up in ether, and treated with ethereal hydrogen chloride to give crystals of 10-[3'-(N-benzoyloxyethylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine dihydrochloride; melting point 226–228° C.

EXAMPLE XX

A suspension of 13.4 g. of 2-trifluoromethylphenothiazine, 2.3 g. of sodium amide and 13.7 g. of 3-chloro-1-(N - methylpiperazinyl) - 2 - (α - tetrahydropyranyloxy)-propane, prepared by reacting dihydropyran with 3 - chloro-2-hydroxy-1-(N-methylpiperazinyl)-propane in 450 ml. of toluene is heated at reflux with stirring for six hours. After working up, following the procedure of Example I, the residue is taken up and warmed on the steam bath with 10% hydrochloric acid for 15 minutes. Neutralization with sodium carbonate, extraction with benzene and evaporation of the solvent gives a viscous syrup. The base is taken up in ethyl acetate and reacted with an excess of maleic acid to give crystals of the dimaleate salt of 10-[2'-hydroxy-3'-(N-methylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine.

EXAMPLE XXI

A suspension of 26.7 g. of 2-trifluoromethylphenothiazine, 25.0 g. of N-carbethoxy-N-(γ -chloro- β -methylpropyl)-piperazine, prepared by condensing N-carbethoxypiperazine with 3-bromo-2-methylpropylchloride, and 4.5 g. of sodium amide in 500 ml. of toluene is reacted and worked up following the procedure of Example II to leave a dark oil, 10-[3'-(N-carbethoxypiperazinyl)-2'-methylpropyl]-2-trifluoromethylphenothiazine.

EXAMPLE XXII

A solution of 28.4 g. of 10-[3'-(N-carbethoxypiperazinyl) - 2' - methylpropyl] - 2 - trifluoromethylphenothiazine (made as in Example XXI) in 300 ml. of aqueous ethanol and 15 ml. of 40% sodium hydroxide solution is heated at reflux for four hours. The alcohol is removed in vacuo and the residue is swirled with benzene and water. The dried benzene layer is evaporated. The thick residue is distilled to give a viscous, yellow oil, 10-(2'-methyl-3'-piperazinylpropyl)-2-trifluoromethylphenothiazine, B.P. 210–215° C. at 0.1 mm. which solidifies upon standing.

A portion of this base, 2.9 g., is dissolved in 75 ml. of

ethyl acetate and reacted with 3 g. of mandelic acid in 50 ml. of ethanol. The mixture is allowed to evaporate on the steam bath until the salt begins to separate. Cooling yields 10-(2'-methyl-3'-piperazinylpropyl)-2-trifluoromethylphenothiazine dimandelate.

A second portion of the base, 2.9 g., is dissolved in 75 ml. of ethyl acetate and mixed with 5 ml. of alcoholic hydrogen bromide. Cooling gives the dihydrobromide salt of the base.

EXAMPLE XXIII

A solution of 5.7 g. of 10-(2'-methyl-3'-piperazinylpropyl)-2-trifluoromethylphenothiazine (made as in Example XXII), in 150 ml. of ethanol is warmed with 1.7 g. of ethylene oxide to 50° C. for one hour. The volatiles are removed in vacuo to leave 10-[3'-(N-hydroxyethylpiperazinyl) - 2' - methylpropyl] - 2 - trifluoromethylphenothiazine.

A solution of 1.6 g. of the base in 50 ml. of ether-benzene is heated at reflux with 1 ml. of acetyl chloride. The separated monohydrochloride of 10-[3'-(N-acetoxyethylpiperazinyl) - 2' - methylpropyl] - 2 - trifluoromethylphenothiazine is optionally isolated as such or shaken in an ethyl acetate-sodium carbonate solution mixture and converted to the dimaleate salt with an excess of maleic acid.

A solution of 1.6 g. of the hydroxyethyl base in 50 ml. of ether-benzene is heated at reflux with 0.8 g. of benzoyl chloride. The hydrochloride of 10-[3'-(N-benzoyloxyethylpiperazinyl) - 2' - methylpropyl] - 2 - trifluoromethylphenothiazine is isolated as described above.

EXAMPLE XXIV

A solution of 2.7 g. of 10-(3'-piperazinylpropyl)-2-trifluoromethylphenothiazine (made as in Example III) and 1.5 g. of benzoyl chloride in 125 ml. of benzene is heated at reflux for several hours. Concentration and standing yields crystals of the hydrochloride of 10-[3'-(N - benzoyloxyethylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine.

Another aliquot containing 2.7 g. of the base and 1.2 g. of 2-furoyl chloride is reacted and worked up as above to yield 10-[3'-(N-furoylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine hydrochloride.

EXAMPLE XXV

A suspension of 36.7 g. of 2-heptafluoropropylphenothiazine (made as in Example XIV), 4.0 g. of sodium amide and 27.5 g. of N-diethylcarbamy-N-(γ-chloropropyl)-piperazine (prepared by reacting N-diethylcarbamy-piperazine with γ-chloropropyl bromide in xylene with sodium amide in 300 ml. of toluene is heated at reflux for six hours. The reaction mixture is worked up following the procedure of Example I, but the hydrochloride salt is recovered and purified by crystallization to give 10 - [3' - (N - diethylcarbamy-piperazinyl) - propyl] - 2 - heptafluoropropylphenothiazine hydrochloride.

EXAMPLE XXVI

A solution of 53.0 g. of crude 10-[3'-N-diethylcarbamy-piperazinyl) - propyl] - 2 - heptafluoropropylphenothiazine hydrochloride (made as in Example XXV) in 200 ml. of concentrated hydrochloric acid is heated at reflux for 10 hours. The solution is diluted with water and filtered. The filtrate is neutralized with 40% sodium hydroxide solution. The separated product is taken up in chloroform, dried and treated with hydrogen chloride gas to separate 2-heptafluoropropyl-10-(3'-piperazinylpropyl)-phenothiazine dihydrochloride.

A suspension of 5.8 g. of this salt in 50 ml. of toluene with 1.8 g. of β-bromoethyl acetate and 2.0 g. of potassium carbonate is heated at reflux, with stirring, for 12 hours. After working up as in Example IV, crystals of 10 - [3' - (N - acetoxyethylpiperazinyl) - propyl] - 2 - heptafluoropropylphenothiazine dihydrochloride are recovered.

EXAMPLE XXVII

A solution of 2.7 g. of 2-trifluoromethylphenothiazine, 2.2 g. of 2-chloro-1-(1',2',3',5',6'-pentamethylpiperazinyl)-ethane and 0.75 g. of sodium amide in 50 ml. of benzene is stirred and heated at reflux for eight hours. After working up as in Example I, micromolecular distillation at 190° C. and 5 microns gives 10-[2'-(1'',2'',3'',5'',6'' - pentamethylpiperazinyl) - ethyl] - 2 - trifluoromethylphenothiazine as a viscous tar.

EXAMPLE XXVIII

A suspension of 2.6 g. of 10-(3'-piperazinylpropyl)-2-trifluoromethylphenothiazine (made as in Example III), 0.5 g. of sodium amide and 1.4 g. of 4-chloro-1-dimethylaminobutane in 50 ml. of toluene is heated at reflux for 24 hours. After working up as in Example I, the viscous base, 10-[3'-(N-dimethylaminobutylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine is recovered.

A solution of 1.0 g. of this base in 50 ml. of ethanol is treated with 0.6 g. of methane sulfonic acid. Trituration with ether and cooling gives the trimethanesulfonate salt.

EXAMPLE XXIX

A suspension of 8.0 g. of 10-(2'-piperazinylethyl)-2-trifluoromethylphenothiazine, 1.8 g. of potassium carbonate and 1.6 g. of allyl chloride in 100 ml. of aqueous ethanol is stirred at reflux for three hours. After working up as described in Example XV, crystals of 10-[2'-(N - allylpiperazinyl) - ethyl] - 2 - trifluoromethylphenothiazine dihydrochloride are obtained.

EXAMPLE XXX

A suspension of 13.4 g. of 2-trifluoromethylphenothiazine, 2.1 g. of sodium amide and 12.5 g. of 3-chloro-1-(N-phenylpiperazinyl)-propane in 250 ml. of toluene is heated at reflux for eight hours. After working up as described in Example I, crystals of 10-[3'-(N-phenylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine maleate are recovered.

EXAMPLE XXXI

A suspension of 26.7 g. of 2-trifluoromethylphenothiazine in 600 ml. of toluene with 4.5 g. of sodium amide is heated at reflux and then reacted for six hours with 35.2 g. of 4-carbobenzoxy-1-ω-chloropropyl)-2,5-diethylpiperazine, prepared by reacting N-carbobenzoxy-2,5-diethylpiperazine with γ-chloropropyl bromide in benzene with sodium amide. The reaction mixture containing 10 - [3' - (N-carbobenzoxy - 2'',5'' - diethylpiperazinyl) - propyl]-2-trifluoromethylphenothiazine is washed with water and treated with dilute hydrochloric acid. The acid extracts are warmed briefly, cooled and treated with sodium hydroxide solution. The separated base is taken up in ethyl acetate, dried and micromolecularly distilled to give the thick base 10-[3'-(2'',5''-diethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine.

A solution of 3.2 g. of the base in 75 ml. of benzene is heated at reflux with 1.2 g. of isocrotonyl chloride with sodium carbonate for several hours. The reaction mixture is treated with dilute hydrochloric acid after neutralization. The product is taken up in ethyl acetate, dried and reacted with maleic acid to give 10-[3'-(N-isocrotonyl - 2'',5'' - diethylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine dimaleate.

Another solution of 3.2 g. of the base in 75 ml. of benzene is reacted with 1.5 g. of dichloroacetyl chloride as above to give the monohydrochloride salt of 10-[3'-(N-dichloroacetyl - 2'',5'' - diethylpiperazinyl) - propyl]-2-trifluoromethylphenothiazine.

A solution of 5.0 g. of the base in 50 ml. of formalin-formic acid mixture is warmed on the steam bath until the evolution of gas ceases. The mixture is neutralized and extracted with dilute hydrochloric acid. The acid extracts

are neutralized, taken up in ethyl acetate and reacted with an excess of hydrogen bromide gas to give 10-[3'-(N-methyl-2'',5''-diethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine dihydrobromide.

EXAMPLE XXXII

A solution of 31.1 g. of 10-[3'-(N-hydroxyethylpiperazinyl)propyl]-2-trifluoromethylphenothiazine in 500 ml. of benzene is prepared as in Example VII. From the stock solution, an aliquot solution containing 3.2 g. of the hydroxyethyl compound is heated briefly at reflux with 1.0 g. of propionyl chloride. A small excess of ethanolic hydrogen chloride is added. The precipitated product is 10-[3'-(N-propionyloxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine dihydrochloride, M.P. 212-214° C.

A second aliquot solution containing 3.2 g. of the hydroxyethyl base is reacted with 1.5 g. of dichloroacetyl chloride as above. The product is 10-[3'-(N-dichloroacetoxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine dihydrochloride.

Another aliquot solution containing 3.2 g. of the hydroxyethyl base is reacted with 1.2 g. of chloroacetyl chloride. The product is 10-[3'-(N-chloroacetoxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine dihydrochloride, M.P. 191-192° C.

Another aliquot solution containing 3.2 g. of the hydroxyethyl base is reacted with 1.5 g. of chloroethyl chloroformate. The product is 10-[3'-(N-chloroethyl-carbonyldioxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine dihydrochloride.

Crotonic chloride, 1.0 g., is reacted with an aliquot of the hydroxyethyl base as above. The separated monohydrochloride of 10-[3'-(N-crotonyloxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine is separated by filtration and washed with ether.

EXAMPLE XXXIII

A suspension of 2.7 g. of 10-(3'-piperazinylpropyl)-2-trifluoromethylphenothiazine (Example III) in 50 ml. of dimethyl formamide with 1.0 g. of potassium carbonate is stirred while 1.3 g. of benzyl chloride is added. The solution is heated at 80° C. for four hours and poured into an excess of water. The resulting precipitate is washed and extracted into benzene. An excess of hydrogen chloride in ethyl acetate gives 10-[3'-(N-benzylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine dihydrochloride.

Another portion of 2.7 g. of the base is reacted with 1.9 g. of phenethyl bromide, as above, to give 10-[3'-(N-phenethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine dihydrochloride.

Another portion (2.7 g.) is alkylated with 2.2 g. of ω -phenylbutyl bromide to give the N- ω -phenylbutyl analogue.

The base (5.4 g.) is alkylated with 2.6 g. of thenyl chloride as above. The dimaleate salt of 10-[3'-(N-thenyl-piperazinyl)-propyl]-2-trifluoromethylphenothiazine is obtained by reacting the crude base with an excess of maleic acid in ethyl acetate solution.

EXAMPLE XXXIV

A solution of 2.8 g. of 10-(2'-methyl-3'-piperazinyl-propyl)-2-trifluoromethylphenothiazine (Example XXII) and 1.6 g. of cyclopentylpropionyl chloride in 50 ml. of benzene is heated at reflux for three hours. The solid separates to give crystals of 10-[3'-(N-cyclopentylpropionylpiperazinyl)-2'-methylpropyl]-2-trifluoromethylphenothiazine hydrochloride.

Another solution of 2.8 g. of the base is reacted with 1.5 g. of hexahydrobenzoyl chloride, as above, to give the hydrochloride of 10-[3'-(N-hexahydrobenzoylpiperazinyl)-2'-methyl-propyl]-2-trifluoromethylphenothiazine.

The base (2.8 g.) is reacted with 2.0 g. of β -cyclo-

hexylethyl bromide in dimethylformamide and 1.0 g. of potassium carbonate is reacted and the product isolated as described in Example XV to give the dimaleate salt of 10-[3'-(N-cyclohexylethylpiperazinyl)-2'-methylpropyl]-2-trifluoromethylphenothiazine.

EXAMPLE XXXV

A solution of 3.4 g. of 10-[3'-(N-hydroxybutylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine (Example XVI) in 25 ml. of benzene is reacted with 2.3 g. of furoyl chloride in 25 ml. of benzene at reflux for two hours. The hydrochloride of 10-[3'-(N-furoyloxybutylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine separates as a crystalline solid.

EXAMPLE XXXVI

A solution of 3.4 g. of the hydroxyethyl base of Example VII is reacted with 1.2 g. of isocaproyl chloride following the procedure above to give the hydrochloride salt of 10-[3'-(N-isocaproxyloxyethylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine as a crystalline solid.

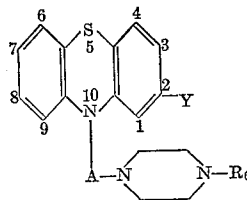
EXAMPLE XXXVII

A suspension of 15.4 g. of 10-(3'-piperazinylpropyl)-2-trifluoromethylphenothiazine in 7.5 ml. of concentrated hydrochloric acid and 100 ml. of water is heated to 85° C. The volume of the reaction mixture is brought to 500 ml. with water. Ethanol (100 ml.) is added along with 3.6 g. of potassium cyanate in 25 ml. of water. After refluxing for one hour, the solvent is removed. The cooled reaction mixture is neutralized with ammonium hydroxide. The suspension is extracted with chloroform. The dried chloroform extract is evaporated to leave crystals of 10-[3'-(N-carbamylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine.

This application is a continuation-in-part of application Serial No. 576,792, filed April 9, 1956, now U.S. Patent No. 2,921,069.

What is claimed is:

1. 10[3'-(4- β -hydroxyethyl piperazinyl) propyl]-2-trifluoromethyl phenothiazine.
2. Chemical compounds of the class consisting of a free base and its nontoxic acid addition salts, the free base having the formula:

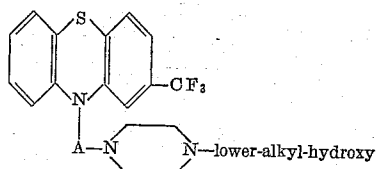


- in which Y is perfluoroalkyl of 1 to 3 carbon atoms; A is an alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms; and R₆ is a member selected from the group consisting of cycloalkyl-lower-alkyl, the cycloalkyl portion having 5 to 6 carbon atoms and the lower-alkyl portion having 1 to 4 carbon atoms, lower alkenyl having 3 to 6 carbon atoms, hydroxy-lower-alkyl having 2 to 6 carbon atoms in the alkyl portion, hydroxy-lower-alkoxy-lower-alkyl, the lower alkyl portions having 2 to 6 carbon atoms, phenyl, phenyl-lower-alkyl having 1 to 6 carbon atoms in the alkyl portion, lower-alkanoyl having 1 to 6 carbon atoms, cycloalkyl-lower-alkanoyl, the cycloalkyl portion having 5 to 6 carbon atoms and the lower-alkanoyl portion having 2 to 4 carbon atoms, phenyl-lower-alkanoyl, the lower alkanoyl portion having 2 to 4 carbon atoms, benzoyl, carbomethoxy, carbethoxy, carbobenzoxy, carbamyl, dialkyl-carbamyl having 1 to 6 carbon atoms in the alkyl portions, N-phenyl-carbamyl, lower-alkanoyloxy-lower-alkyl, the lower-alkanoyloxy portion having 2 to 6 carbon atoms and the lower-alkyl portion having 2 to 6 carbon atoms and benzoyloxy-lower-alkyl

15

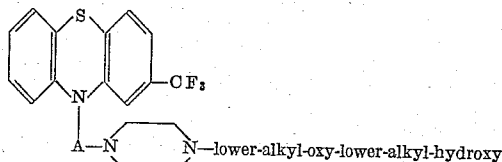
having 2 to 6 carbon atoms in the lower alkyl portion.

3. A chemical compound of the formula:



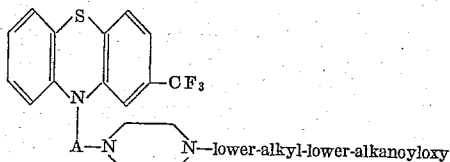
in which A is an alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms and the lower-alkyl portion has 2 to 6 carbon atoms.

4. A chemical compound of the formula:



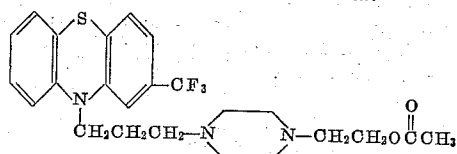
in which A is an alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms and each of the lower-alkyl portions have 2 to 6 carbon atoms.

5. A chemical compound of the formula:

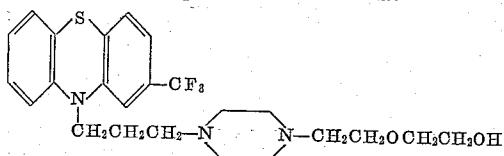


in which A is an alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms; the lower-alkyl portion having 2 to 6 carbon atoms and the lower-alkanoyloxy portion having 2 to 6 carbon atoms.

6. A chemical compound of the formula:

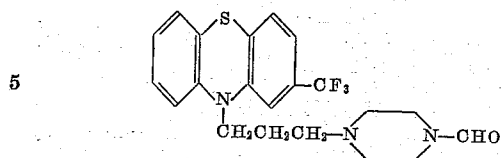


7. A chemical compound of the formula:

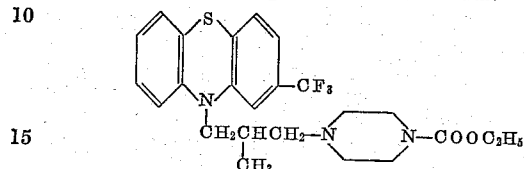


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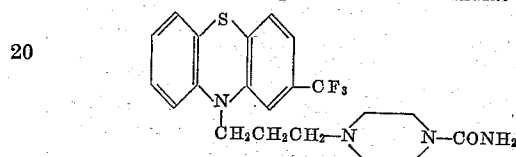
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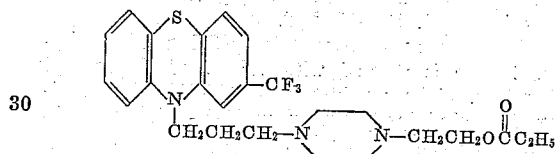
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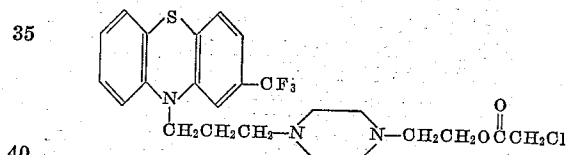
10. A chemical compound of the formula:



11. A chemical compound of the formula:



12. A chemical compound of the formula:



References Cited in the file of this patent

UNITED STATES PATENTS

2,766,235	Cusic	Oct. 9, 1956
2,902,485	Horclois	Sept. 1, 1959
2,921,069	Uillyot	Jan. 12, 1960

FOREIGN PATENTS

293/55	South Africa	Aug. 22, 1955
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