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SUBSTITUTED ARALKYL PHENOTHIAZINYL-ALKYL PIPERAZINES

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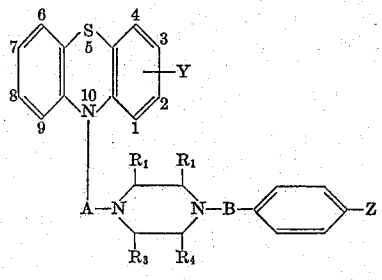
5 Claims. (Cl. 260—243)

This invention relates to new substituted 1-aralkyl-4-(10-phenothiazinylalkyl)-piperazines of value as medicinal agents. More specifically, the compounds of this invention have utility as tranquilizers, antiemetics sedatives, antihitaminics, anticonvulsants and potentiators of various central nervous system depressants, such as analgetics or anesthetics. Of particular importance are the utilities of these compounds as tranquilizers and antiemetics. The high potency of these compounds affords therapeutic benefits at relatively low doses.

In addition, these compounds, particularly those containing a trifluoromethyl moiety, have chemotherapeutic or antimicrobial activity, such as antileprosy, antitubercular, antibacterial and antifungal activity. For example, they possess antifungal or antibacterial activity, such as against *Diplococcus pneumoniae* Type I, *Hemolytic streptococcus, Micrococcus pyogenes* var. *aureus, Klebsiella pneumoniae* and *Candida albicans.* Further, these compounds have anthelmintic activity.

The substituted 1-aralkyl-4-(10-phenothiazinylalkyl)-piperazines of this invention are represented by the following general formula:

Formula 1



when:

Y represents hydrogen, chlorine, trifluoromethyl, methyl, methoxy, trifluoromethoxy, acetyl, trifluoroacetyl, methylmercapto, trifluoromethylmercapto, methylsulfonyl, trifluoromethylsulfonyl, or cyano;

A represents a divalent, straight or branched alkylene chain containing from 2 to 4 carbon atoms, separating the two nitrogens to which it is attached by at least two carbon atoms;

R_1, R_2, R_3, and R_4 represent hydrogen, methyl, or ethyl;

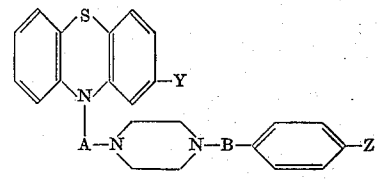
R represents a divalent, straight or branched alkylene or alkenyl chain, the alkylene chain containing from 1 to 4 carbon atoms and the alkenyl chain containing from 3 to 4 carbon atoms; and

Z represents amino, mono methylamino, dimethylamino, acylamino such as alkanoylamino, the alkanoyl moiety containing from 2 to 6 carbon atoms, for example acetylamino, or benzoylamino, methoxy, or methylmercapto. The compounds in which Z represents a nitro group also have utility as intermediates as indicated hereafter.

The Y moiety is preferably in the 2 position of the phenothiazine ring.

Advantageous compounds of this invention are represented by the following structural formula:

Formula 2



when:

Y represents chlorine, trifluoromethyl, trifluoro methoxy, trifluoroacetyl, methylmercapto, trifluoromethyl mercapto, methylsulfonyl, trifluoromethylsulfonyl, or cyano;

A represents a divalent, straight or branched alkylene chain containing from 2 to 4 carbon atoms, separating the two nitrogens to which it is attached by at least two carbon atoms;

B represents a divalent, straight or branched alkylene or alkenyl chain, the alkylene chain containing from 1 to 4 carbon atoms and the alkenyl chain containing from 3 to 4 carbon atoms; and

Z represents amino, mono methylamino, dimethylamino, acetylamino, benzoylamino, methoxy, or methylmercapto.

Preferred compounds of this invention are represented by Formula 2 when:

Y represents trifluoromethyl;

A represents a divalent, straight or branched alkylene chain containing from 2 to 4 carbon atoms, separating the two nitrogens to which it is attached by at least two carbon atoms;

B represents a divalent straight or branched alkylene or alkenyl chain, the alkylene chain containing from 1 to 3 carbon atoms and the alkenyl chain containing 3 carbon atoms; and

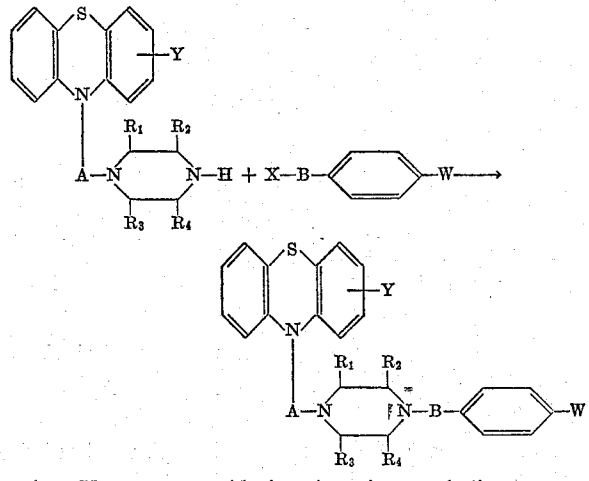
Z represents amino, acetylamino, or benzoylamino.

By the term "aralkyl" where used herein alone or in combination with other terms, phenylalkyl or phenylalkenyl groups having less than 10 carbon atoms are indicated. The term "acyl" is used to include carbon-containing radicals of organic carboxylic acids, such as alkanoyl containing from 2 to 6 carbon atoms, for example acetylamino, or benzoyl. Where used herein the term "alkylene" represents a saturated aliphatic carbon chain and the term "alkenyl" represents an aliphatic carbon chain containing a double bond. When the alkylene chain represents a branched carbon chain, the alkylene chain contains from 2 to 4 carbon atoms; and when the alkenyl chain represents a branched carbon chain, the alkenyl chain contains 4 carbon atoms.

This invention also includes salts of the above defined bases formed with nontoxic pharmaceutically acceptable organic and inorganic acids. Such salts are easily pre-

pared 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, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids as well as with the 8-halotheophyllines, for example, 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, 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 novel substituted 1-aralkyl-4-(10-phenothiazinylalkyl)-piperazines of this invention are prepared by alkylating substituted 10-piperazinylalkyl phenothiazines with a substituted aralkyl halide as represented by the following reaction:



when X represents chlorine, bromine, or iodine;

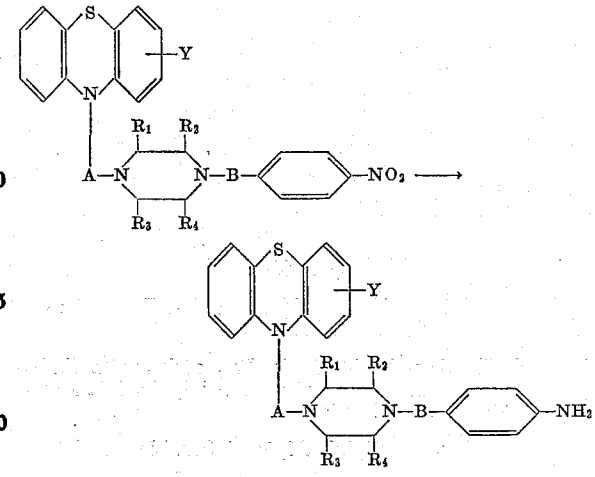
Y, A, R_1, R_2, R_3, R_4, and B are as defined above; and

W represents nitro, mono methylamino, dimethylamino, acylamino, methoxy or methylmercapto.

The alkylation is carried out advantageously by heating the reactants in a suitable inert aromatic solvent such as, preferably, a lower-carbon amide, for example dimethylformamide. The reaction mixture is heated at from about 90–150° C. for from 3 to 15 hours, preferably 4 to 8 hours. The substituted 1-aralkyl-4-(10-phenothiazinylalkyl)-piperazine is isolated by cooling the reaction mixture and pouring it into an excess of water. The mixture is made alkaline with dilute sodium hydroxide solution and extracted with chloroform. The dried chloroform extracts are evaporated to yield a residue which may be an oily base or a crystalline solid. The oily base is often purified by fractional distillation under high vacuum; the crystalline solid is recrystallized for purification. In practice the basic oil is dissolved in an organic solvent and converted to a stable acid addition salt by reaction with a suitable organic or inorganic acid.

The above alkylation procedure is alternatively carried out by suspending the piperazinyl phenothiazine in an aqueous solution of an alkali metal hydroxide, for example sodium hydroxide, and adding the aralkyl halide. After standing for from 12 to 36 hours, the product is isolated by extraction with an organic solvent as described above or, if solid, by filtration.

In the above alkylation methods, the nitro substituted 1-aralkyl-4-(10-phenothiazinylalkyl)-piperazines (W is nitro) are further reacted to yield the amino substituted compounds included in the general Formula 1.



Y, A, R_1, R_2, R_3, R_4 and B are defined above. The nitro substituted compounds are reduced advantageously by shaking a solution of the compound in a lower carbon alcohol, preferably ethanol, under hydrogen pressure in the presence of a catalyst such as platinum oxide for from 30 minutes to several hours. The catalyst is removed by filtration and the filtrate evaporated to give the primary amino derivative as an oily residue which is readily converted to a stable acid addition salt as described previously.

Alternatively, the nitro substituted 1-aralkyl-4-(10-phenothiazinylalkyl)-piperazines are reduced catalytically by employing Raney nickel in an ethanol solution or chemically by employing an active metal such as iron or tin in acid solution, for example hydrochloric acid solution.

An alternative method for the preparation of acylamino substituted 1-aralkyl-4-(10-phenothiazinylalkyl)-piperazines utilizes the primary amino derivatives prepared as above. Thus, the primary amino derivative is further treated with an acyl halide, preferably a chloride, in a solution of a suitable inert organic solvent such as benzene, toluene, or xylene, and usually in the presence of an alkali metal carbonate, for example sodium or potassium carbonate. The reaction mixture is allowed to stand at ambient temperature for from 8 to 15 hours or alternatively, is refluxed for from 2 to 15 hours. Upon filtration and removal of the solvent, the acylamino product is obtained.

The substituted 10-piperazinylalkyl phenothiazines are prepared advantageously by alkylating the substituted phenothiazine with an ω-haloalkylpiperazine having the free N-hydrogen of the piperazinyl moiety replaced by an easily removed moiety, for example, a benzyl, formyl, carbobenzoxy, carbomethoxy or carbethoxy group. The carbethoxy group is preferred. The alkylation is carried out advantageously by refluxing an ω-haloalkylpiperazine, preferably chloro or bromo, and a substituted phenothiazine in a suitable inert aromatic solvent such as, preferably, benzene, toluene or xylene, in which at least one of the reactants must be soluble. A suitable acid-binding agent is usually included, such as an alkali metal amide, preferably sodium, potassium or lithium amide. The reaction mixture is refluxed for from 3 to 18 hours and worked up after cooling by adding an excess of water, extracting with dilute hydrochloric acid, neutralizing with base and extracting with benzene. Evaporation of the benzene extracts yields the residual base. The N-protective group is then removed under mild conditions, such as by alkaline hydrolysis with for example sodium hydroxide solution, in the case of the preferred carbethoxy group.

Another synthetic route to 10-piperazinylalkyl pheno-

thiazines is by means of 10-(ω-ester-alkyl)-phenothiazines which have a reactive end group on the 10-alkyl chain, for example an ω-tosylate or ω-chloro end group, which can be reacted with a piperazine having one N-hydrogen replaced by an easily removed moiety as described above. For example, the ester and piperazine are refluxed in the presence of an acid-binder for a short period and further worked up as described above.

The substituted phenothiazines are prepared following known methods. Thus, a substituted 2-halo-2'-aminodiphenyl sulfide is cyclized in the presence of an acid-binding agent, for example sodium or potassium carbonate, and catalytic amounts of copper or copper bronze powder, by refluxing in dimethylformamide for from 6 to 18 hours.

A different synthetic approach to the preparation of the susbtituted phenothiazines utilized substituted diphenylamines. In this method, the substituted diphenylamine is heated with sulfur in the presence of a catalytic amount of iodine with or without a solvent at from 120 to 230° C. for from one to four hours.

The foregoing is a general description of the main synthetic routes in the preparation of substituted 1-aralkyl-4-(10-phenothiazinylalkyl)piperazines. 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 methods thoroughly discussed above, namely, alkylation of substituted 10-piperazinylalkyl-phenothiazines with a substituted aralkyl halide and alkylation of substituted phenothiazines in the 10-position of the nucleus by an ω-haloalkyl-piperazine having the free N-hydrogen of the piperazine moiety replaced by an easily removed moiety.

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 may be present as optical isomers. The connotation of the general formulae presented therein is to include all isomers, particularly 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, for instance, of the *d*-tartrate salts of the substituted 1-aralkyl-4-(10-phenothiazinylalkyl)-piperazine derivatives. Alternatively, a synthesis starting with an optically active side chain may yield the desired optical isomer.

The following examples are not limiting but are 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 1

A suspension of 26.7 g. of 2-trifluoromethylphenothiazine (Belgian Patent 551,400) and 4.0 g. of sodium amide in 300 ml. of toluene is refluxed with rapid stirring for 15 minutes. A solution of 25.8 g. of N-carbethoxy-N'-(3-chloropropyl)-piperazine in 100 ml. of toluene is added and refluxing continued for six hours. The cooled reaction mixture is treated with 100 ml. of water and the toluene layer is extracted with dilute hydrochloric acid. The acid extracts are made basic with ammonia and then extracted with benzene. The benzene is removed by distillation in vacuo to yield the residual 10-[3-(N-carbethoxypiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine.

A solution of 21.0 g. of 10-[3-(N-carbethoxypiperazinyl)-propyl]-2-trifluoromethylphenothiazine in 75 ml. of ethanol and 50 ml. of water containing 5 ml. of 40% sodium hydroxide solution is heated at reflux for two hours. The ethanol is distilled off in vacuo on the steam bath. The residue is treated with benzene-water and the dried organic layer evaporated in vacuo to give 10-(3-piperazinylpropyl)-2-trifluoromethylphenothiazine.

To a solution of 7.9 g. of 10-(3-piperazinylpropyl)-2-trifluoromethylphenothiazine in 25 ml. of dimethylformamide is added a solution of 5.1 g. of p-nitrophenethyl bromide in 30 ml. of dimethylformamide. After stirring at 95–105° C. for six and one-half hours, the solution is cooled and poured into 1 l. of water. The mixture is made alkaline with 10% sodium hydroxide solution and is extracted with chloroform. The combined chloroform extracts are washed with water, dried over potassium carbonate and then filtered. The solvent is removed from the filtrate to yield 1-(p-nitrophenethyl)-4-[3-(2-trifluoromethyl-10-phenothiazinyl)-propyl]-piperazine as a dark oil.

The oily base is converted by treatment with two equivalents of maleic acid in ethyl acetate solution to the dimaleate salt which after recrystallization melted at 176.5–178.5° C.

Example 2

A mixture of 5.4 g. of 1-(p-nitrophenethyl)-4-[3-(2-trifluoromethyl - 10 - phenothiazinyl)-propyl]-piperazine (prepared as in Example 1) dissolved in 100 ml. of warm ethanol and 0.3 g. of platinum oxide is shaken over 50 p.s.i. of hydrogen for one hour. The catalyst is filtered and washed with ethanol. The ethanol solutions are combined and the solvent is removed in vacuo on the steam bath. The residual oil, 1-(p-aminophenethyl)-4-[3 - (2 - trifluoromethyl - 10 - phenothiazinyl) - propyl]-piperazine, is converted to the trihydrochloride salt, M.P. 241–242.5° C.

A solution of 10.2 g. of the above amino compound and 1.6 g. of acetyl chloride in 75 ml. of benzene is heated on the steam bath for three hours. Evaporaiton of the mixture to dryness under reduced pressure gives 1-(p-acetamidophenethyl)-4-[3 - (2 - trifluoromethyl-10-phenothiazinyl)-propyl]-piperazine hydrochloride.

Example 3

To a stirred suspension of 12.8 g. of 10-(3-piperazinylpropyl)-2-trifluoromethylphenothiazine (prepared as in Example 1) in a solution of 3.0 g. of sodium hydroxide in 50 ml. of water, is added 9.2 g. of p-nitrobenzyl chloride, in portions. The resulting gummy mixture is stirred at room temperature overnight. The yellow crystalline product, 1 - (p - nitrobenzyl)-4-[3-(2-trifluoromethyl-10-phenothiazinyl)-propyl]-piperazine, is filtered and then purified by recrystallization, M.P. 110–111.5° C.

Example 4

To a solution of 9.7 g. of 1-(p-nitrobenzyl)-4-[3-(2-trifluoromethyl - 10 - phenothiazinyl) - propyl] - piperazine (prepared as in Example 3) in 150 ml. of hot absolute ethanol is added 0.2 g. of platinum oxide. The resulting suspension is shaken with hydrogen on a Parr hydrogenator; the initial hydrogen pressure was 15 lbs./in.^{2}. The calculated amount of hydrogen is taken up in 30 minutes. The catalyst is filtered and the almost colorless filtrate is concentrated to dryness under reduced pressure. The residual pale yellow oil is crystallized by treatment with a few drops of ether to yield 1-(p-aminobenzyl)-4-[3-(2-trifluoromethyl-10-phenothiazinyl) - propyl] - piperazine, M.P. 118.5–121° C.

A solution of the free base (5.6 g.) in 40 ml. of absolute methanol is treated with a solution of 4.0 g. of maleic acid in 57 ml. of acetone to furnish the dimaleate salt, M.P. 148–150° C. dec.

A solution of the free base (5.0 g.) and 1.4 g. of benzoyl chloride in 100 ml. of benzene is refluxed for several hours. Concentrating the reaction mixture yields 1-(p-benzamidobenzyl) - 4 - [3 - (2 - trifluoromethyl - 10-phenothiazinyl)-propyl]-piperazine hydrochloride.

Example 5

A mixture of 10.0 g. of phenothiazine, 2.1 g. of soda-

mide and 14.4 g. of N-carbethoxy-N'-(3-chloropropyl)-2,5-dimethylpiperazine (prepared by reacting the N-carbethoxy derivative of 2,5-dimethylpiperazine with 1-bromo-3-chloropropane) in 200 ml. of toluene is heated at reflux with stirring for eight hours. The cooled reaction mixture is worked up as in Example 1 to give 10-[3-(N-carbethoxy-2,5-dimethylpiperazinyl)-propyl]-phenothiazine.

A solution of 4.3 g. of the above phenothiazine derivative in 25 ml. of ethanol and 15 ml. of water containing 1 ml. of 40% sodium hydroxide solution is refluxed for two hours. The solvent is removed and the reaction mixture further treated as described in Example 1 to yield 10-[3-(2,5-dimethylpiperazinyl)-propyl]-phenothiazine.

A solution of 5.0 g. of 1-bromo-3-(p-methoxyphenyl)-propane in 25 ml. of dimethylformamide is added to a solution of 7.1 g. of 10-[3-(2,5-dimethylpiperazinyl)-propyl]-phenothiazine in 50 ml. of dimethylformamide. The resulting solution is stirred and heated at 100–105° C. for six hours, cooled and then worked up as in Example 1. The base which is thus obtained, 1-(p-methoxyphenylpropyl)-4-[3-(10-phenothiazinyl)-propyl]-2,5-dimethylpiperazine, is converted to the dihydrochloride salt.

Example 6

A mixture of 5.8 g. of 2-chlorophenothiazine (U.S. Patent 2,645,640), 0.6 g. of lithium amide and 6.8 g. of N-carbethoxy-N'-(3-chloro-2-methylpropyl)-piperazine (prepared from the reaction of N-carbethoxypiperazine and 1-bromo-3-chloro-2-methylpropane) in 150 ml. of toluene is refluxed for eight hours and then worked up as in Example 1 to yield 10-[3-(N-carbethoxypiperazinyl)-2-methylpropyl]-2-chlorophenothiazine.

An ethanolic solution of 13.3 g. of the above-prepared phenothiazine with 30 ml. of water containing 3 ml. of 40% sodium hydroxide solution is refluxed for two hours. Removal of the solvent and treating the reaction mixture as described in Example 1 furnishes 2-chloro-10-(2-methyl-3-piperazinylpropyl)-phenothiazine.

A solution of 9.3 g. of 2-chloro-10-(2-methyl-3-piperazinylpropyl)-phenothiazine and 7.0 g. of p-acetamidocinnamyl bromide (prepared by treating p-nitrocinnamyl alcohol with phosphorus tribromide, reducing the bromide with tin and hydrochloric acid and acetylating the p-aminocinnamyl bromide with acetyl chloride) in 100 ml. of dimethylformamide is heated at 100° C. for eight hours. Upon working up the reaction mixture as in Example 1, 1-(p-acetamidocinnamyl)-4-[3-(2-chloro-10-phenothiazinyl)-2-methylpropyl]-piperazine is isolated.

Treating the free base with an ethyl acetate solution of bismethylene salicylic acid yields the bismethylene salicylate salt.

Example 7

A solution containing 11.3 g. of 10-(2-piperazinylethyl)-2-trifluoromethylphenothiazine (Belgian Patent 551,400) and 5.7 g. of p-methylmercaptobenzyl chloride in 125 ml. of dimethylformamide is stirred and heated at 95–100° C. for seven hours. The cooled reaction mixture is treated with water and made alkaline with dilute sodium hydroxide solution. The alkaline solution is extracted with chloroform and the extracts washed with water. The combined dried extract is evaporated in vacuo to yield 1-(p-methylmercaptobenzyl)-4-[2-(2-trifluoromethyl-10-phenothiazinyl)-ethyl]-piperazine.

The base is reacted with anhydrous hydrogen bromide gas in an ether solution to give the dihydrobromide salt.

Example 8

A suspension of 7.5 g. of 2-methylphenothiazine (U.S. Patent 2,785,160), 1.4 g. of sodamide and 7.3 g. of N-formyl-N'-(3-chloropropyl)-piperazine in 175 ml. of toluene is stirred and heated at reflux for eight hours. Water is added to the cooled reaction mixture, the organic layer separated and then extracted with dilute mineral acid. The acid extracts are made basic with ammonia and extracted with benzene. Removal of the solvent yields 10-[3-(N-formylpiperazinyl)-propyl]-2-methylphenothiazine. The formyl group is hydrolyzed in aqueous ethanol with 40% sodium hydroxide solution as outlined in Example 1.

A solution of 10.0 g. of 2-methyl-10-(3-piperazinylpropyl)-phenothiazine (obtained from above) and 8.0 g. of 1-bromo-2-methyl-3-(p-methoxyphenyl)propane in 250 ml. of dimethylformamide is stirred and heated at 95–100° C. for eight hours. The cooled reaction mixture is treated as described in Example 1 to yield 1-[2-methyl-3-(p-methoxyphenyl)-propyl]-4-[3-(2-methyl-10-phenothiazinyl)-propyl]-piperazine.

Example 9

A solution of 9.2 g. of 2-methoxyphenothiazine (U.S. Patent 2,785,160) in 125 ml. of toluene is alkylated with 10.0 g. of N-carbethoxy-N'-(3-chloropropyl)-piperazine in the presence of 1.6 g. of sodium amide to yield 10-[3-(N-carbethoxypiperazinyl)-propyl]-2-methoxyphenothiazine. This latter compound is then refluxed in an aqueous ethanol solution containing 40% sodium hydroxide solution to hydrolyze the carbethoxy group.

A solution of 8.9 g. of 2-methoxy-10-(3-piperazinylpropyl)-phenothiazine (prepared above) and 5.4 g. of 3-chloro-1-(p-methylaminophenyl)-butene-1 [prepared by reducing p-nitrostyryl methyl ketone under Meerwein Ponndorf conditions of isopropanol and aluminum i-propoxide to give the nitro alcohol, converting the alcohol to the chloride by means of thionyl chloride, reducing the thus formed 3-chloro-1-(p-nitrophenyl)-butene-1 with tin and hydrochloric acid to the amino compound and then alkylating with methyl iodide in the presence of potassium carbonate] in 150 ml. of dimethylformamide is stirred and heated at 95–105° C. for seven hours. Treating the reaction mixture as in Example 1 and evaporating the chloroform extracts yields 1-[1-methyl-3-(p-methylaminophenyl)-2-propenyl]-4-[3-(2-methoxy-10-phenothiazinyl)-propyl]-piperazine.

Example 10

A stirred suspension of 67.5 g. of chlorobenzene and 80.0 g. of aluminum chloride is cooled to −10° C. and 66.3 g. of trifluoroacetyl chloride is added. When the addition is complete, the mixture is allowed to stand at room temperature overnight. The reaction mixture is then poured onto ice and water, and extracted with ether. The dried ether extracts are evaporated to give 4-chloro-α,α,α-trifluoroacetophenone.

A mixture of 31.5 g. of concentrated nitric acid and 49.0 g. of concentrated sulfuric acid, cooled to 0° C., is added slowly to 20.8 g. of 4-chloro-α,α,α-trifluoro-alpha-acetophenone. The mixture is stirred for three hours at 5° C. and then poured onto ice. The solid is filtered, washed with water and recrystallized to yield 4-chloro-3-nitro-α,α,α-trifluoroacetophenone.

A solution of 25.3 g. of 4-chloro-3-nitro-α,α,α-trifluoroacetophenone in 250 ml. of ethanol is added to a mixture of 4.0 g. of sodium hydroxide in 25 ml. of water and 18.9 g. of o-bromothiophenol in 300 ml. of ethanol. The suspension is refluxed for one hour and filtered hot. The filtrate yields 4-(2'-bromophenylmercapto)-3-nitro-α,α,α-trifluoroacetophenone upon dilution with a small amount of water and cooling.

A solution of 112.8 g. of stannous chloride crystals in 300 ml. of concentrated hydrochloric acid is carefully mixed with 20.3 g. of 4-(2'-bromophenylmercapto)-3-nitro-α,α,α-trifluoroacetophenone. The mixture is stirred and refluxed for three hours. The cooled reaction mixture is made alkaline, refluxed for 30 minutes and then extracted with benzene. The solvent is removed by distillation in vacuo and upon purification of the residue, 3-

amino - 4(2' - bromophenylmercapto) - α,α,α - trifluoroacetophenone is obtained.

A suspension of 18.8 g. of 3-amino-4-(2'-bromophenylmercapto)-α,α,α-trifluoroacetophenone, 7.3 g. of anhydrous potassium carbonate and 0.7 g. of copper-bronze powder in 175 ml. of dimethylformamide is heated at reflux with stirring for 15 hours under a stream of nitrogen. The cooled reaction mixture is filtered and the filtrate diluted with water. The solid which thus forms is vacuum sublimed and recrystallized to give pure 2-phenothiazinyl trifluoromethyl ketone.

A mixture of 11.8 g. of phenothiazinyl trifluoromethyl ketone, 1.6 g. of sodamide and 10.0 g. of N-carbethoxy-N'-(2-chloropropyl)-piperazine in 150 ml. of toluene is refluxed with stirring for eight hours. The cooled reaction mixture is treated as described in Example 1 to yield 10-[2-(N-carbethoxypiperazinyl)-isopropyl]-2-trifluoroacetylphenothiazine. The carbethoxy group is hydrolyzed by refluxing in aqueous ethanol with 40% sodium hydroxide solution for one hour.

A solution of 16.8 g. of 10-(2-piperazinylisopropyl)-2-trifluoroacetylphenothiazine (prepared above) and 8.9 g. of p-methoxybenzyl bromide in 200 ml. of dimethylformamide is heated at 95° C. for five hours. The cooled solution is treated with water, made alkaline with dilute sodium bicarbonate solution and then extracted with chloroform. The chloroform extracts are washed with water, dried and evaporated in vacuo to yield 1-(p-methoxybenzyl) - 4-[2 - (2 - trifluoroacetyl - 10 - phenothiazinyl)-isopropyl]-piperazine.

The free base is treated with mandelic acid in ethyl acetate solution to furnish the dimandelate salt.

Example 11

A mixture of 15.7 g. of nitric acid and 24.5 g. of sulfuric acid, cooled to 0° C., is added slowly to 8.8 g. of 4-aminophenyl trifluoromethyl ether. The mixture is stirred for three hours at 5° C. and then poured onto ice. The solid is filtered, washed with water and recrystallized from ethanol to yield 3-nitro-4-aminophenyl trifluoromethyl ether.

Following the general Sandmeyer procedure, 3-nitro-4-aminophenyl trifluoromethyl ether is diazotized in hydrochloric acid with sodium nitrite at 0° C. and a solution of one equivalent of cuprous chloride in hydrochloric acid is added. The complex is decomposed in the usual manner by warming a suspension of this substance and the oily layer which separates is steam distilled to give 3-nitro-4-chlorophenyl trifluoromethyl ether.

A solution of 2.0 g. of sodium hydroxide pellets in 15 ml. of water is added to a solution of 9.5 g. of 2-bromothiophenol in 125 ml. of ethanol and the mixture added to 12.1 g. of 3-nitro-4-chlorophenyl trifluoromethyl ether dissolved in 75 ml. of ethanol. The resulting mixture is heated at reflux for three hours and filtered while hot. The solid removed by filtration is washed several times with hot ethanol. Diluting the combined ethanolic solutions with water and cooling furnishes 2'-bromo-2-nitro-4-trifluoromethoxydiphenyl sulfide.

A solution of 225.7 g. of stannous chloride crystals in 750 ml. of concentrated hydrochloric acid is mixed with 39.4 g. of 2'-bromo-2-nitro-4-trifluoromethoxydiphenyl sulfide. The mixture is stirred and refluxed for five hours, cooled and filtered. The complex is refluxed for hour with 10% sodium hydroxide solution and then washed with benzene. The organic layer is removed and the residue washed several times with benzene. The combined benzene washes are evaporated in vacuo to yield after purification, 2'-bromo-2-amino-4-trifluoromethoxydiphenyl sulfide.

A suspension of 36.4 g. of 2'-bromo-2-amino-4-trifluoromethoxydiphenyl sulfide, 15.9 g. of anhydrous potassium carbonate and 1.5 g. of copper-bronze powder in 300 ml. of dimethyl formamide is flushed with nitrogen and refluxed with stirring for 18 hours under a stream of nitrogen. The cooled reaction mixture is filtered and quenched in 1 l. of water. The solid thus obtained is purified by recrystallization and sublimation to give crystals of 2-trifluoromethoxyphenothiazine.

A suspension of 6.2 g. of 2-trifluoromethoxyphenothiazine in 100 ml. of toluene is alkylated with 7.0 g. of N-carbethoxy-N'-(3-chloropropyl)-2,5-diethylpiperazine in the presence of 0.9 g. of sodium amide to give 10-[3-(N-carbethoxy-2,5-diethylpiperazinyl)-propyl]-2-trifluoromethoxyphenothiazine. The latter compound is hydrolyzed with 40% sodium hydroxide solution.

The thus formed 10-[3-(2,5-diethylpiperazinyl)-propyl]-2-trifluoromethoxyphenothiazine (14.0 g.) dissolved in 75 ml. of dimethylformamide is treated with 5.6 g. of p-dimethylaminobenzyl chloride dissolved in 50 ml. of dimethylformamide and the resulting solution is heated at 105° C. for eight hours. Working up as described in Example 1, the product 1-(p-dimethylaminobenzyl)-4-[3 - (2 - trifluoromethoxy-10-phenothiazinyl)-propyl]-2,5-diethylpiperazine is obtained.

Example 12

A mixture of 3.1 g. of 2-acetyl-10-(3-chloropropyl)-phenothiazine (South African Patent 2,798), 0.4 g. of sodium amide and 1.8 g. of N-carbethoxypiperazine in 150 ml. of toluene is stirred and refluxed for eight hours. The cooled reaction mixture is worked up as in Example 1 to yield 2-acetyl-10-[3-(N-carbethoxypiperazinyl)-propyl]-phenothiazine.

A solution of 13.1 g. of 2-acetyl-10-[3-(N-carbethoxypiperazinyl)-propyl]-phenothiazine in 50 ml. of ethanol and 30 ml. of water containing 3 ml. of 40% sodium hydroxide solution is refluxed for two hours. Working up the reaction mixture as in Example 1 yields 2-acetyl-10-(3-piperazinylpropyl)-phenothiazine.

A solution of 11.0 g. of 2-acetyl-10-(3-piperazinylpropyl)-phenothiazine and 5.6 g. of p-methoxyphenethyl chloride in 200 ml. of dimethylformamide is heated at 95–105° C. with stirring for eight hours. The cooled solution is worked up as in Example 1 to yield 1-(p-methoxyphenethyl) - 4 - [3-(2-acetyl-10-phenothiazinyl)-propyl]-piperazine.

The free base is treated with ethereal hydrogen chloride to give the dihydrochloride salt.

Example 13

A suspension of 4.9 g. of 2-methylmercaptophenothiazine (Belgian Patent 552,836) and 0.8 g. of sodium amide in 75 ml. of toluene is refluxed and stirred for 30 minutes. A solution of 5.2 g. of N-carbethoxy-N'-(3-chloropropyl)-piperazine in 50 ml. of toluene is added and refluxing continued for eight hours. The cooled reaction mixture is treated as in Example 1 to yield 10-[3-(N-carbethoxypiperazinyl) - propyl]-2-methylmercaptophenothiazine. A solution of the phenothiazine in aqueous ethanol in the presence of 40% sodium hydroxide solution is refluxed for two hours to give the hydrolysis product, 2 - methylmercapto - 10 - (3-piperazinylpropyl)-phenothiazine.

A solution of 7.9 g. of 3-(p-butyramidophenyl)-1-chloropropane [prepared from the acylation of 3-(p-aminophenyl)-1-chloropropane with butyryl chloride] in 50 ml. of dimethylformamide is added to a solution of 11.1 g. of 2-methylmercapto-10-(3-piperazinylpropyl)-phenothiazine in 75 ml. of dimethylformamide and the mixture stirred and heated at 95–105° C. for seven hours. Working up as outlined in Example 1 yields 1-[3-(p-butyramidophenyl) - propyl]-4-[3-(2-methylmercapto-10-phenothiazinyl)-propyl]-piperazine.

By reacting the free base dissolved in acetone with an acetone solution of citric acid, the dicitrate salt is formed.

Example 14

To a solution of 284.5 g. of 3-bromophenyl methyl

sulfide in 1425 ml. of dry chloroform at 10° C., dry chlorine is introduced while the solution is irradiated with a 150 watt lamp. The reaction mixture is maintained at 15–18° C. for six and one-half hours. The reaction is stopped and a vigorous stream of nitrogen is introduced. The solvent is removed under reduced pressure and the residue distilled to give a yellow oil, 3-bromophenyl trichloromethyl sulfide, B.P. 102–104° C./1.1 mm.

A mixture of 142.0 g. of 3-bromophenyl trichloromethyl sulfide and 110.0 g. of antimony trifluoride is heated in a distillation flask and the fraction boiling at 190–205° C. is collected. This fraction is dissolved in 800 ml. of ether and washed several times with 6 N hydrochloric acid and then water. The ether solution is dried and the solvent removed under reduced pressure. Distillation at atmospheric pressure yields a colorless liquid, 3-bromophenyl trifluoromethyl sulfide, B.P. 192–194° C.

A mixture of 160.0 g. of 3-bromophenyl trifluoromethyl sulfide, 100.0 g. of acetanilide, 52.9 g. of anhydrous potassium carbonate and 2.1 g. of copper-bronze powder is heated in an oil bath at a bath temperature of 220–230° C. for 24 hours. The cooled dark brown viscous mass is extracted with 750 ml. of acetone and the solvent removed under reduced pressure. To the dark brown residue, 180 ml. of concentrated hydrochloric acid in 515 ml. of ethanol is added. The mixture is refluxed for five hours and allowed to stand at room temperature over night. It is then poured into 2.5 liters of cold water and made just alkaline with 20% sodium hydroxide. Extraction with ether and removal of the dried solvent under reduced pressure gives a dark residue which is vacuum distilled to yield a pale yellow oil, 3-trifluoromethylmercaptodiphenyl amine, B.P. 115–119° C./0.3 mm.

A mixture of 117.0 g. of 3-trifluoromethylmercaptodiphenyl amine, 25.0 g. of sulfur and 1.8 g. of iodine is heated in an oil bath at 145–160° C. for one and one-half hours under a stream of nitrogen. The cooled reaction mass is dissolved in one liter of boiling benzene and treated with chromatographic alumina and charcoal. Concentration of the filtrate gives a solid, 2-trifluoromethylmercaptophenothiazine, which recrystallizes from carbon tetrachloride as yellow plates, M.P. 165–166° C.

A mixture of 29.9 g. of 2-trifluoromethylmercaptophenothiazine, 4.1 g. of sodamide and 25.7 g. of N-carbethoxy-N'-(3-chloropropyl)-piperazine is stirred and heated at reflux for eight hours. Working up the reaction mixture as in Example 1 yields 10-[3-(N-carbethoxypiperazinyl) - propyl] - 2-trifluoromethylmercaptophenothiazine which is hydrolyzed by heating for 90 minutes in an aqueous ethanol solution containing slightly less than one equivalent of sodium hydroxide.

A solution of 21.3 g. of 10-(3-piperazinylpropyl)-2 - trifluoromethylmercaptophenothiazine (prepared as above) and 13.3 g. of p-acetamidophenethyl bromide in 250 ml. of dimethylformamide is stirred and heated at 95–100° C. for seven hours. The cooled reaction mixture is treated with water and worked up further according to the procedure in Example 1 to yield 1-(p-acetamidophenethyl) - 4 - [3-(2-trifluoromethylmercapto-10-phenothiazinyl)-propyl]-piperazine.

An ethereal solution of the free base is treated with anhydrous hydrogen chloride gas to give the dihydrochloride salt.

Example 15

A mixture of 6.9 g. of 2-methylsulfonylphenothiazine (Belgian Patent 556,475), 1.0 g. of sodamide and 8.0 g. of 3 - chloro - 1 - (N-carbethoxy - 2,3,5,6 - tetramethylpiperazinyl)-propane in 150 ml. of toluene is heated at reflux for 10 hours. Cooling and working up as in Example 1 yields 10-[3-(N-carbethoxy-2,3,5,6-tetramethylpiperazinyl)-propyl]-2-methylsulfonylphenothiazine. The latter compound is hydrolyzed by refluxing for two hours an aqueous ethanolic solution with 40% sodium hydroxide solution.

A solution of 4.6 g. of 2-methylsulfonyl-10-[3-(2,3,5,6-tetramethylpiperazinyl)-propyl]-phenothiazine (prepared as above) and 2.4 g. of p-methylaminophenethyl bromide (prepared by the alkylation of p-aminophenethyl bromide with methyl iodide) in 50 ml. of dimethylformamide is heated at 105° C. for seven hours. Working up the reaction mixture as in Example 1 yields 1-(p-methylaminophenethyl) - 4 - [3-(2-methylsulfonyl-10-phenothiazinyl)-propyl]-2,3,5,6-tetramethylpiperazine.

Example 16

A solution of 8.0 g. of chromic anhydride, 8.0 g. of sulfuric acid and 25 ml. of water is mixed with 15.4 g. of 3-nitro-4-chlorophenyl trifluoromethyl sulfide and the resulting mixture is stirred for 15 hours at 120–130° C. Steam distilling the reaction mixture yields 3-nitro-4-chlorophenyl trifluoromethyl sulfone.

A solution of 4.0 g. of sodium hydroxide pellets in 30 ml. of water is added to 18.9 g. of 2-bromothiophenol dissolved in 250 ml. of ethanol and the resulting mixture added to a solution of 28.9 g. of 3-nitro-4-chlorophenyl trifluoromethyl sulfone in 100 ml. of ethanol. The suspension is refluxed for three hours. The solid present is filtered from the hot reaction mixture and washed several times with hot ethanol. The combined alcoholic filtrate is diluted with a small amount of water and cooled to yield 2'-bromo-2-nitro-4-trifluoromethylsulfonyldiphenyl sulfide.

A solution of 225.7 g. of stannous chloride crystals in 750 ml. of concentrated hydrochloric acid is carefully mixed with 44.2 g. of 2'-bromo-2-nitro-4-trifluoromethylsulfonyldiphenyl sulfide. The mixture is stirred and refluxed for five hours. The cooled reaction mixture is filtered and the separated solid metal complex is broken up by hydrolysis for one hour at reflux with 10% caustic soda and washed with benzene. The organic layer is separated and combined with further benzene washes. The solvent is then removed by distillation in vacuo and upon purification of the residue, 2'-bromo-2-amino-4-trifluoromethylsulfonyldiphenyl sulfide is obtained.

A suspension of 20.6 g. of 2'-bromo-2-amino-4-trifluoromethylsulfonyldiphenyl sulfide, 8.3 of anhydrous potassium carbonate and 0.4 g. of copper-bronze powder in 200 ml. of dimethylformamide is stirred and heated at reflux for 18 hours. The cooled reaction mixture is filtered and the filtrate diluted with water. The solid which thus forms is vacuum sublimed at 0.05 mm. (175–195° C.) and recrystallized to give pure 2-trifluoromethylsulfonylphenothiazine.

A mixture of 3.3 g. of 2-trifluoromethylsulfonylphenothiazine, 0.4 g. of sodium amide and 2.6 g. of N-carbethoxy-N'-(3-chloropropyl)-piperazine in 100 ml. of toluene is heated at reflux for eight hours. The cooled reaction mixture is worked up following Example 1 to give 10-[3-(N-carbethoxypiperazinyl)-propyl]-2-trifluoromethylsulfonylphenothiazine.

A solution of 5.3 g. of 10-[3-(N-carbethoxypiperazinyl)-propyl]-2-trifluoromethylsulfonylphenothiazine in 30 ml. of ethanol and 10 ml. of water containing 1 ml. of 40% sodium hydroxide solution is refluxed for 90 minutes. Removing the solvent and treating as in Example 1 gives 10-(3-piperazinylpropyl)-2-trifluoromethylsulfonylphenothiazine.

A solution of 4.6 g. of 10-(3-piperazinylpropyl)-2-trifluoromethylsulfonylphenothiazine and 2.0 g. of 2-chloro-1-(p-methoxyphenyl)-propane [prepared by the addition of hydrogen chloride to p-allylphenol to give 2-chloro-1-(p-hydroxyphenyl)-propane which is then converted to the sodium salt and alkylated with dimethylsulfate] in 50 ml. of dimethylformamide is stirred and heated at 95–105° C. for seven hours. Working up the reaction mixture yields 1-[2-(p-methoxyphenyl)-isopropyl]-4-[3-(2-

trifluoromethylsulfonyl - 10 - phenothiazinyl) - propyl]-piperazine.

Example 17

A mixture of 4.5 g. of 2-cyanophenothiazine (Belgian Patent 552,557), 0.8 g. of sodium amide and 5.2 g. of N-carbethoxy-N'-(3-chloropropyl)-piperazine in 100 ml. of toluene is stirred and refluxed for eight hours. Working up as in Example 1 yields 10-[3-(N-carbethoxy-piperazinyl)-propyl]-2-cyanophenothiazine. The latter compound is hydroyzed by refluxing an aqueous ethanol solution with 40% sodium hydroxide solution.

A solution of 3.5 g. of 2-cyano-10-(3-piperazinyl-propyl)-phenothiazine (prepared as above) and 3.3 g. of p-benzamidophenethyl bromide in 75 ml. of dimethylformamide is stirred and heated at 100° C. for seven hours. Working up the reaction mixture as in Example 1 yields 1-(p-benzamidophenethyl)-4-[3-(2-cyano-10-phenothiazinyl)-propyl]-piperazine.

Example 18

A solution of 2.7 g. of 1-bromo-3-(p-nitrophenyl)-propane in 15 ml. of dimethylformamide is added to a solution of 3.9 g. of 10-(3-piperazinylpropyl)-2-trifluoromethylphenothiazine (prepared as in Example 1) in 15 ml. of dimethylformamide and the resulting solution is stirred and heated at 95–105° C. for seven hours. Upon working up the reaction mixture as described in Example 1, the product 1-[3-(p-nitrophenyl)-propyl]-4-[3-(2-trifluoromethyl-10-phenothiazinyl)-propyl]-piperazine is obtained.

Example 19

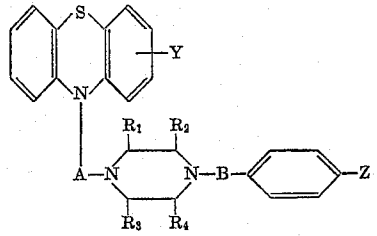
A mixture of 5.6 g. of 1-[3-(p-nitrophenyl)-propyl]-4-[3 - (2 - trifluoromethyl - 10 - phenothiazinyl) - propyl]-piperazine (prepared as in Example 18) and 0.3 g. of platinum oxide in 150 ml. of warm ethanol is hydrogenated for one hour. Treating the mixture as in Example 2 yields 1-[3-(p-aminophenyl)-propyl]-4-[3-(2-trifluoromethyl-10-phenothiazinyl)-propyl]-piperazine.

A stirred suspension of the above amino compound (5.3 g.), 1.2 g. of isovaleryl chloride and 1.5 g. of potassium carbonate in 50 ml. of xylene is refluxed for five hours. The reaction mixture is treated with water and the separated xylene layer is extracted with dilute hydrochloric acid. The acid extracts are neutralized and extracted with benzene. The solvent is removed in vacuo to give 1-[3-p-isovaleramidophenyl)-propyl]-4-[3 - (2 - trifluoromethyl - 10 - phenothiazinyl) - propyl]-piperazine.

Similarly, acylating as above with isocaproyl chloride yields 1-[3-(p-isocapramidophenyl)-propyl]-4-[3-(2-trifluoromethyl-10-phenothiazinyl)-propyl]-piperazine.

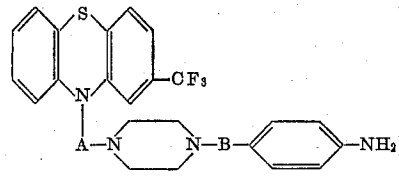
What is claimed is:

1. A chemical compound of the class consisting of a free base and its nontoxic acid addition salts, said free base having the formula



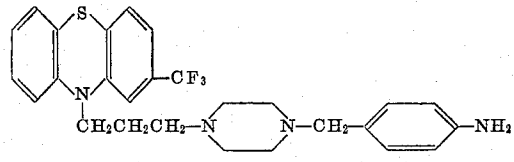
in which Y is a member selected from the group consisting of hydrogen, chlorine, trifluoromethyl, methyl, methoxy, trifluoromethoxy, acetyl, trifluoroacetyl, methylmercapto, trifluoromethylmercapto, methylsulfonyl, trifluoromethylsulfonyl, and cyano; A is a divalent alkylene chain containing 2 to 4 carbon atoms, separating the two nitrogens to which it is attached by at least two carbon atoms; R_1, R_2, R_3, and R_4 are members selected from the group consisting of hydrogen, methyl, and ethyl; B is a member selected from the group consist- of a divalent alkylene chain containing 1 to 4 carbon atoms and a divalent alkenyl chain containing 3 to 4 carbon atoms; and Z is a member selected from the group consisting of amino, mono methylamino, dimethylamino, alkanoylamino containing 2 to 6 carbon atoms, benzoylamino, nitro, methoxy, and methylmercapto.

2. A chemical compound having the basic structural formula:

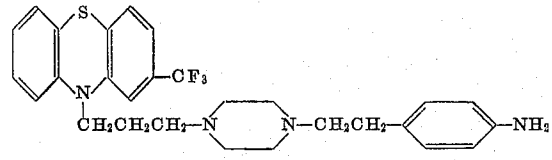


in which A is a divalent alkylene chain of from 2 to 4 carbon atoms, separating the two nitrogen atoms to which it is attached by at least two carbon atoms; and B is a divalent alkylene chain of from 1 to 3 carbon atoms.

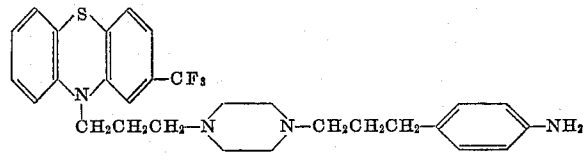
3. A chemical compound having the basic structural formula:



4. A chemical compound having the basic structural formula:



5. A chemical compound having the basic structural formula:



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