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1-(4-AMINO-2-PERFLUOROALKYL-5-PYRIMIDINYLMETHYL) PIPERAZINES

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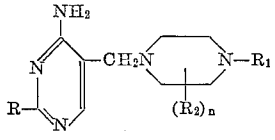
This invention relates generally to new chemical compounds and to methods of preparing them. It relates further to new compounds which are useful in treating and preventing the poultry disease coccidiosis. More particularly, it is concerned with novel piperazine compounds. Still more specifically, it is concerned with 1-(4 - amino-2-trifluoromethyl-5-pyrimidinylmethyl)-piperazines, 1 - (4-amino-2-perfluoroethyl-5-pyrimidinylmethyl)-piperazines, to acid addition salts thereof and to methods of preparing such compounds. It relates in addition to animal feed compositions containing such compounds.

In accordance with the present invention, it has now been discovered that certain 1-(4-amino-2-fluoroethyl-5-pyrimidinylmethyl)-piperazines and their acid addition salts possess a high degree of activity against the poultry disease coccidiosis. It is one object of the present invention to provide such compounds. An additional object is provision of a method of synthesizing such piperazines. A still further object is the provision of compositions which are useful in the treatment or prevention of coccidiosis and which contain the novel piperazines as an active ingredient. Further objects will become clear from the following description of the invention.

The class of compounds embraced by this invention are 1 - (4-amino - 2-fluoroalkyl-5-pyrimidinylmethyl)-piperazines wherein the piperazine ring may be further substituted with a lower alkyl or lower alkenyl radical, and acid addition salts of such piperazines. This class of compounds, which may be represented by Formula I below, has a generally high level of anticoccidial activity.



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In the above structural formula, R is a trifluoromethyl (CF_3) or perfluoroethyl (C_2F_5) group, R_1 is hydrogen, a lower alkyl or a lower alkenyl group, R_2 is a lower alkyl radical, and n is a whole integer having a value of 0–2 inclusive. It is preferred that the lower alkyl groups represented by R_2 contain from 1–3 carbon atoms, e.g. methyl, ethyl and propyl radicals, although other lower alkyl groups such as butyl and amyl may be employed if desired. R_1 in these new compounds may be hydrogen, or it may be a lower alkyl or lower alkenyl radical of the type represented by methyl, ethyl, propyl, allyl and isopropyl. Although the preferred compounds of the invention are those wherein n is 0, substances of Formula I having 1 or 2 lower alkyl groups attached to the carbon atoms of the piperazine ring are within the purview of the invention.

These 1 - (4-amino-2-fluoroalkyl-5-pyrimidinylmethyl)-piperazines readily form acid addition salts which may contain up to 2 moles of acid per mole of piperazine. Although the invention is not limited to particular acid addition salts, for the purpose of treating coccidiosis it is preferred to employ a non-toxic salt, typical examples of which are mineral acid salts such as the hydrochloride, hydrobromide, sulfate and phosphate salts and salts of organic acids such as citrate, tartrate and naphthalene

disulfonate salts. Although the di-acid salt is formed when an excess of acid is used, those skilled in this art will realize that mixtures of mono- and di-acid salts are obtained when a theoretical deficiency of acid is present.

The substances of the invention may be obtained by intimately contacting an appropriate piperazine with a 4-amino-2-fluoroalkyl-5-hydroxymethyl pyrimidine ester of a strong inorganic acid, such as a hydrohalic acid. As the pyrimidine reactant a 4-amino-2-fluoroalkyl-5-halomethyl pyrimidine is preferred. Such halomethyl pyrimidines are normally produced synthetically in the form of acid addition salts and it is convenient to use such salts as starting materials. For this reason, we prefer to employ an inorganic base or an excess of piperazine to neutralize the excess acid. The novel compounds of the invention are formed by the reaction of equimolar amounts of the piperazine and pyrimidine reactants so that excess piperazine or inorganic base is not necessary if the 4-amino-2-fluoroalkyl-5-halomethyl pyrimidine is utilized in the form of its free base.

The reaction is conveniently conducted in an inert solvent medium. An excess of the liquid piperazine may be used as the reaction medium if desired. It proceeds satisfactorily at room temperature, although higher or lower temperatures could be employed without affecting the process adversely. Since one mole of hydrogen halide is formed as a reaction product, an acid addition salt forms unless an excess of piperazine or an inorganic base such as sodium or potassium carbonate is present to neutralize this acid. The resulting 1-(4-amino-2-fluoroalkyl-5-pyrimidinylmethyl)-piperazine is conveniently recovered by quenching the reaction mixture in water and extracting the desired product into an organic solvent such as chloroform, benzene or ether. It has been found that the free bases are more easily purified than the acid addition salts and it is, therefore, a preferred embodiment of the process to make the mixture strongly alkaline after the reaction is completed and to recover the 1-substituted piperazines in the form of the free base. They may be conveniently converted to any desired acid addition salt by treating with an excess of the appropriate acid in a suitable solvent, such as methanol, ethanol or ether.

According to a second aspect of the invention, the 1-(4-amino-2-fluoroalkyl - 5 - pyrimidinylmethyl)-4-lower alkyl (or 4-lower alkenyl) piperazines described herein may be obtained by first reacting piperazine with 4-amino-2-fluoroalkyl-5-halomethyl pyrimidine to form 1-(4-amino-2-fluoroalkyl-5-pyrimidinylmethyl) - piperazine, and treating this material with an alkylating agent, such as a lower alkyl or lower alkenyl halide.

When used for the prevention of coccidiosis, the compounds of the invention are normally fed to poultry as a component of the feed of the animals although they may also be given dissolved or suspended in the drinking water. According to one aspect of the invention, novel compositions are provided in which a 1-(4-amino-2-fluoroalkyl-5-pyrimidinylmethyl)-piperazine of Formula I above, or an acid addition salt thereof, is present as an active anticoccidial ingredient. Such compositions comprise the piperazine compound intimately dispersed in or admixed with an inert carrier or diluent, i.e. a diluent that is nonreactive with the piperazine and may be administered with safety to the animals. The carrier or diluent is preferably one that is or may be an ingredient of the animal feed.

The compositions which are a preferred feature of the invention are the so-called feed supplements in which the active ingredient is present in relatively large amounts and which are suitable for addition to the poultry feed either directly or after an intermediate dilution or blending step. Examples of carriers or diluents suitable for

such compositions are solid orally ingestible carriers such as distillers' dried grains, corn meal, molasses solubles, Attapulgus clay, wheat shorts, fermentation residues, citrus meal, ground oyster shells, corn cob meal, antibiotic mycelia, edible vegetable substances, soybean mill feed, crushed limestone, soya grits, toasted dehulled soya flour and the like. The piperazines are intimately dispersed or admixed throughout the solid inert carrier by methods such as grinding, stirring, milling or tumbling. By selecting proper diluents and by altering the ratio of carrier to active ingredient, compositions of any desired concentration may be prepared. Formulations containing from about 1% to about 40% by weight, and preferably from about 2–25% by weight of active ingredient are particularly suitable for addition to poultry feeds. The active compound is normally dispersed or mixed uniformly in the diluent but in some instances may be sorbed on the carrier. Examples of typical feed supplements containing a 1-(4-amino-2-fluoroalkyl-5-pyrimidinylmethyl)-piperazine dispersed in a solid inert carrier are:

A.	Lbs.
1-(4 - amino-2-perfluoroethyl-5-pyrimidinylmethyl)-4-ethyl piperazine	25.0
Wheat standard middlings	75.0

B.	
1-(4-amino - 2 - trifluoromethyl-5-pyrimidinylmethyl)-4-methyl piperazine	10.0
Corn distillers' dried grains	90.0

C.	
1-(4 - amino-2-perfluoroethyl-5-pyrimidinylmethyl)-4-propyl piperazine	15.0
Molasses solubles	85.0

D.	
1-(4-amino - 2 - trifluoromethyl-5-pyrimidinylmethyl)-piperazine	20.0
Corn germ meal	30.0
Corn distillers' grains	50.0

These and similar feed supplements are prepared by uniformly mixing the active compound with the carrier or carriers.

Such feed supplements are usually further diluted with materials such as corn meal or soybean meal before being incorporated in the animal feed. In this intermediate processing step the level of coccidiostat in the carrier is brought down to from about 0.1% to about 1.0% by weight. This dilution serves to facilitate uniform distribution of the substance in the finished feed. The finished feed is one that contains a source of fat, protein, carbohydrate, minerals, vitamins and other nutritional factors.

The amount of 1-(4-amino-2-fluoroalkyl-5-pyrimidinylmethyl)-piperazine required for control of coccidiosis in poultry will, of course, vary somewhat with the specific compound or compounds employed. The compounds of Formula I above generally are effective in preventing the disease when administered at levels of less than about 0.05% by weight of the feed. With the preferred compounds of the invention, i.e. those where R_1 in Formula I is lower alkyl and $n=0$, good prevention of coccidiosis is obtained by administering to the poultry from about 0.0005% to about 0.05% by weight of the total feed consumed; for most satisfactory results it is preferred that the poultry feed contain between about 0.003% and 0.025% by weight of piperazine compound. The compounds may also be dissolved or suspended in the drinking water of the poultry and administered by this route.

The following examples are given for the purposes of illustration and not by way of limitation.

EXAMPLE 1

1-(4-Amino-2-Perfluoroethyl-5-Pyrimidinylmethyl)-4-Ethyl Piperazine

15 g. of N-ethyl piperazine in 50 ml. of acetonitrile is added slowly to a mixture of 20 g. of 4-amino-2-perfluoroethyl-5-pyrimidinylmethyl bromide hydrobromide in 75 ml. of acetonitrile. The mixture is shaken and allowed to stand at room temperature for 18 hours. 300 ml. of water and 25 ml. of concentrated ammonium hydroxide is then added to the reaction mixture. The resulting solution is extracted with 4 x 100 ml. of chloroform. The resulting chloroform extracts are combined and washed with water. The chloroform solution is then evaporated to dryness in vacuo to give a residue of 1-(4-amino-2-perfluoroethyl-5-pyrimidinylmethyl)-4-ethyl piperazine. On recrystallization from ether-petroleum ether, there is obtained substantially pure material, M.P. 138–140° C.

EXAMPLE 2

1-(4-Amino-2-Trifluoromethyl-5-Pyrimidinylmethyl)-4-n-Propyl Piperazine

To 50 g. of 4-n-propyl piperazine in 300 ml. of ethanol is added 100 g. of 4-amino-2-trifluoromethyl-5-bromomethylpyrimidine hydrobromide. The resulting mixture is warmed until all the solid material dissolves and then allowed to stand at room temperature for 15 hours. It is then cooled and any precipitate removed by filtration. The filtrate is concentrated in vacuo to about one-third its volume and made strongly basic with 2.5 N aqueous sodium hydroxide solution. The alkaline solution is extracted with 2 x 150 ml. of chloroform. The chloroform extracts are combined, washed with 100 ml. of water and concentrated to dryness in vacuo. On crystallization of the solid from hot benzene there is obtained substantially pure 1-(4-amino-2-trifluoromethyl-5-pyrimidinylmethyl)-4-n-propyl piperazine.

EXAMPLE 3

1-(4-Amino-2-Perfluoroethyl-5-Pyrimidinylmethyl)-Piperazine

25 g. of 4-amino-2-perfluoroethyl - 5 - bromoethylpyrimidine hydrobromide is added slowly to a solution of 25 g. of piperazine hexahydrate in 150 ml. of ethanol. The mixture is warmed to dissolve the solids and then allowed to stand at room temperature for 10 hours. It is then cooled in an ice bath and any solid piperazine hydrobromide removed by filtration. The solution is then concentrated to a volume of 40 ml. and made strongly alkaline with dilute aqueous sodium hydroxide. It is then extracted with 2 x 25 ml. of chloroform. The chloroform extracts are combined, washed with water and concentrated to dryness in vacuo. The residual 1-(4-amino-2-perfluoroethyl-5-pyrimidinylmethyl) - piperazine is purified by recrystallization from hot xylene.

The material obtained immediately above is converted to 1-(4-amino-2 - perfluoroethyl-5 - pyrimidinylmethyl)-4-ethyl piperazine in the following manner:

0.8 g. of the above compound and 0.4 g. of ethyl iodide are refluxed for 90 minutes in 10 ml. of ethyl alcohol. The ethyl alcohol is then removed by evaporation and the residue made alkaline with 2.5 N aqueous sodium hydroxide. The resulting aqueous solution is extracted twice with an equal volume of ether. The ether extracts are combined and concentrated to dryness in vacuo to form 1-(4-amino-2 - perfluoroethyl-5-pyrimidinylmethyl)-4-ethyl piperazine.

EXAMPLE 4

1-(4-Amino-2-Trifluoromethyl-5-Pyrimidinylmethyl)-4-Ethyl Piperazine

To a stirred suspension of 65 g. of anhydrous sodium carbonate and 325 ml. of acetonitrile is added 40 g. of N-methyl piperazine. 135 g. of 4-amino-2-trifluoro-

methyl-5-bromomethylpyrimidine hydrobromide is added to this suspension slowly over a period of 45 minutes. The resulting reaction mixture is stirred for 12 hours at room temperature. 300 ml. of water is then added and the resulting solution concentrated under vacuum to remove the organic solvent. The alkaline aqueous solution is extracted with 5 x 25 ml. of chloroform. The chloroform extracts are combined and concentrated to dryness in vacuo. The solid thus obtained is extracted with 200 ml. of ether and the ether solution treated with a small amount of decolorizing charcoal. The charcoal is filtered off and the ether solution concentrated to about one-half its volume. Substantially pure 1-(4-amino-2-trifluoromethyl-5-pyrimidinylmethyl)-4-ethyl piperazine is crystallized by the addition of petroleum ether to the above ether solution.

The 2-fluoroalkyl-4-amino - 5 - halomethyl pyrimidines which are used as one of the starting materials in carrying out this invention may be prepared in the following manner:

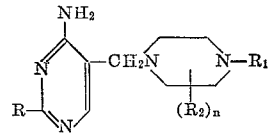
5 g. of 2-trifluoromethyl-4 - amino-5 - hydroxymethyl pyrimidine is dissolved in 30 ml. of a 30% solution of hydrogen bromide in acetic acid. The resulting mixture is heated at 70 °C. for 6 hours and then allowed to stand at room temperature for 15 hours. The crystalline 2-trifluoromethyl-4-amino-5-bromomethyl pyrimidine hydrobromide which forms is recovered by filtration, washed with ether and dried. When the above reaction is carried out with an equimolar amount of 2-perfluoroethyl-4-amino-5-hydroxymethyl pyrimidine there is obtained 2-perfluoroethyl-4-amino-5-bromomethyl pyrimidine hydrobromide. The chloromethyl pyrimidines may be utilized in this process in place of the bromomethyl pyrimidines, and such substances are obtained either via metathesis of the bromo compound using an anion exchange resin on the chloride cycle, or by treatment of the 5-hydroxymethyl pyrimidine with hydrochloric acid.

The 2-trifluoromethyl-4-amino - 5 - hydroxymethyl pyrimidine may be prepared as described by Barone et al. in J. Org. Chem. 24 199 (1959). Barone et al. describe the preparation of the above compound starting with perfluoroacetamidine. When perfluoropropionamidine is utilized in this process in place of perfluoroacetamidine, there is obtained 2-perfluoroethyl-4 - amino-5-hydroxymethyl pyrimidine. Perfluoropropionamidine may be prepared as described in U.S. Patent No. 2,676,985.

Any departure from the above description which conforms to the present invention is intended to be included within the scope of the claim.

What is claimed is:

1. A member of the class consisting of a compound of the formula



wherein R is selected from the class consisting of trifluoromethyl and perfluoroethyl groups, R_1 is selected from the class consisting of hydrogen, lower alkyl and lower alkenyl, R_2 is a lower alkyl group and n has a value of 0–2 inclusive, and non-toxic addition salts thereof.

2. A non-toxic acid addition salt of 1-(4-amino-2-trifluoromethyl-5-pyrimidinylmethyl) - 4-loweralkyl piperazine.

3. 1-(4 - amino - 2 - trifluoromethyl - 5 - pyrimidinylmethyl)-4-loweralkyl piperazine.

4. 1-(4-amino - 2-perfluoroethyl-5-pyrimidinylmethyl)-4-loweralkyl piperazine.

5. 1-(4-amino - 2 - trifluoromethyl - 5 - pyrimidinylmethyl)-4-ethyl piperazine.

6. A non-toxic addition salt of 1-(4-amino-2-perfluoroethyl-5-pyrimidinylmethyl)-4-ethyl piperazine.

7. 1-(4-amino-2-perfluoroethyl - 5-pyrimidinlymethyl)-4-ethyl piperazine.

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