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BENZODIOXANE DERIVATIVES

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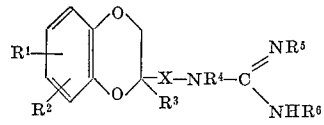
4 Claims. (Cl. 260—309.6)

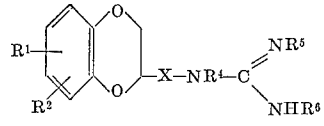
This invention relates to new and useful compounds in the field of organic heterocycle chemistry. More particularly, it is concerned with various novel 2-guanidinoalkyl-1,4-benzodioxane compounds which have been found to be useful as therapeutic agents in view of the biological properties which they possess.

The compounds which are included within the purview of the present invention are all selected from the class of organic bases having the following general structural formula:



and the mineral and organic acid addition salts thereof, wherein each of R^1 and R^2 is a member chosen from the group consisting of hydrogen, chlorine, bromine, iodine, alkyl and alkoxy each having up to six carbon atoms; each of R^3 and R^4 is a member chosen from the group consisting of hydrogen and alkyl containing up to six carbon atoms; X is a member chosen from the group consisting of $-(CH_2)_n-$, CH_2NH and CH_2CH_2NH wherein n is an integer of from one to six; and each of R^5 and R^6 is a member chosen from the group consisting of hydrogen, alkyl containing up to six carbon atoms, acyl containing from two to six carbon atoms, and when taken together with the nitrogen atoms to which they are attached, form part of a heterocyclic ring. These compounds are all of value in the treatment of hypertension.

Of especial value in this connection, and as a matter of fact the preferred compounds of this invention, are those of the formula:



and the mineral and organic acid addition salts thereof, wherein each of R^1 and R^2 is a member chosen from the group consisting of hydrogen, chlorine, bromine, lower alkyl and lower alkoxy; X is a member chosen from the group consisting of lower alkylene, CH_2NH and CH_2CH_2NH; R^4 is a member chosen from the group consisting of hydrogen and lower alkyl; and each of R^5 and R^6 are members chosen from the group consisting of hydrogen and lower alkyl and, when taken together with the nitrogen atoms to which they are attached and the carbon atom which is geminal to said nitrogen atoms, imidazolyl. Typical member compounds of this series include such 2-guanidinoalkyl - 1,4 - benzodioxanes as 2 - guanidinomethyl - 1,4 - benzodioxane, 2-guanidinomethyl-6,7-dichloro - 1,4 - benzodioxane, 2-(3-guanidinopropyl)-1,4-benzodioxane, 2 - guanidinoaminomethyl-1,4-benzodioxane, 2-(1-methylguanidino)methyl-1,4-benzodioxane, 2-(N,N' - ethyleneguanidinomethyl)-1,4-benzodioxane, and the like.

The process employed for preparing the novel compounds of this invention involves treating an appropriately substituted 2-aminoalkyl-1,4-benzodioxane compound with a suitable S-alkyl isothiouronium salt having the requisite substituent groups. This particular reaction is

normally carried out in a reaction-inert polar solvent medium at a temperature ranging from about 20° C. up to about 150° C. for a period of about one to about 72 hours. In practice, it is generally most convenient to heat the two reactants together under reflux in the polar solvent, employing substantially equimolar amounts of starting materials for this purpose although a slight excess of one or the other is not harmful in this respect. The desired S-allyl isothiouronium salt reagent, of course, is preferably one where the S-alkyl group is lower alkyl in view of relative ease with which such a reaction takes place due to the more volatile nature of the by-products produced, i.e., the lower boiling mercaptans. Preferred reaction-inert polar solvents for use in this connection include water, lower alkanols, such as methanol, ethanol and isopropanol, etc., and N,N-di(lower alkyl)alkanoamides such as N,N-dimethylformamide, N,N-dimethylacetamide, N,N-diethylformamide, N,N-diethylacetamide, N,N - di(n - propyl)formamide, N,N-dimethylpropionamide, and so forth, as well as mixtures of either of these two aforementioned type organic solvents with water. Upon completion of the reaction, the solvent is removed by means of conventional procedures and the resulting residue taken up in a suitable solvent system, such as one of the aforementioned types, from which it can be subsequently crystallized. Alternatively, the product may separate first from the reaction mixture either during the course of the reaction or immediately therefater, or it may be crystallized from the reaction solution after some initial concentration of same. A final conversion to the desired organic base compound can then be effected by treating the 2-guanidinoalkyl-1,4-benzodioxane acid addition salt thus obtained with sufficient base in water to neutralize same, e.g., an alkaline reagent such as sodium hydroxide in water can be used. Recovery of the desired free organic base can then be had by extracting the aforesaid aqueous solution with a suitable water-immiscible organic solvent of low volatility, such as a halogenated aliphatic hydrocarbon solvent like methylene chloride, for example.

The starting materials necessary for the above reaction process are either all known compounds or else they are easily prepared by those skilled in the art in accordance with standard organic procedures. For instance, the 2-aminoalkyl-1,4-benzodioxanes can easily be prepared by known routes starting from the corresponding 2-haloalkyl-1,4-benzodioxanes, which are, in turn, prepared via ring-closure of the appropriate catechol compounds with reagents such as epichlorohydrin, etc. The corresponding S-alkyl isothiouronium salts, such as S-methyl isothiouronium sulfate, and so on, are, of course, members of a well-known class of organic compounds.

Other methods which can be used to prepare the novel compounds of this invention include routes not involving the use of the S-alkyl isothiouronium intermediates and these are as follows: (1) the reaction of a 2-sulfonyloxyalkyl-1,4-benzodioxane compound with the appropriate guanidine salt to afford the corresponding 2-guanidinoalkyl-1,4-benzodioxane salt direct; (2) the reaction of said sulfonyloxy compound with ammonia or with phthalimide and water, and the subsequent conversion of the resulting 2-aminoalkyl-1,4-benzodioxane intermediate to the desired product by treatment with either the appropriate guanidinopyrazole salt or with dicyandiamide; (3) the reaction of a 2-sulfonyloxyalkyl-1,4-benzodioxane with a metallo azide to form the corresponding organic azide, followed by reduction of the latter compound to the aforementioned 2-aminoalkyl-1,4-benzodioxane intermediate which can then be treated as before; (4) the reaction of a 2-aminoalkyl-1,4-benzodioxane compound with cyanamide to form the corresponding 2-guanidinoalkyl-1,4-benzodioxane; (5) the reaction of said amino-

alkyl compound with a cyanogen halide, followed by reaction of the resultant product with an appropriate amine; and finally, (6) the reaction of a 1,4-benzodioxane-2-alkylcarboxyaldehyde with an appropriately substituted guanidine, followed by reduction of the resultant hydrazone intermediate.

Of these alternate routes, the most preferred one is the first mentioned process involving the reaction of a 2-sulfonyloxyalkyl-1,4-benzodioxane, such as 2-(p-toluene sulfonyloxy)methyl-1,4-benzodioxane, with a guanidine salt such as the hydrochloride to form the corresponding 2-guanidinoalkyl-1,4-benzodioxane sulfonate salt direct. This process is generally carried out by heating the two reactants together in an alcoholic solvent medium (usually, at steam bath temperatures) in the presence of a basic condensing agent like sodium hydride, for example. Recovery of the desired product from the reaction mixture is then easily effected by means of evaporation under reduced pressure, followed by subsequent crystallization of the resulting residue from water.

Insofar as the 2-guanidinoalkyl-1,4-benzodioxane compounds of this invention are basic compounds, they are capable of forming a wide variety of salts with various mineral and organic acids. Although such salts must be pharmaceutically acceptable when the final products are intended for oral consumption, it is possible to first isolate the desired 2-guanidinoalkyl-1,4-benzodioxane compound from the reaction mixture as a pharmacetuically unacceptable salt and then to subsequently convert the latter, as indicated previously, to the free base by treatment with an alkaline reagent, followed by the final conversion to the pharmaceutically acceptable acid salt in the manner hereinafter indicated. For instance, the acid addition salts of the 2 - guanidinoalkyl - 1,4 - benzodioxane compounds of this invention may be prepared by treating the base compound with a substantially equimolar amount of the chosen acid. The salt-formation step can be carried out in an aqueous solution or in a suitable organic solvent such as methanol or ethanol. Upon careful evaporation of the solvent, the solid salt is obtained.

The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned 2-guanidinoalkyl-1,4-benzodioxane bases of this invention are those which form non-toxic acid addition salts containing pharmaceutically acceptable anions, such as the hydrochloride, hydrobromide, hydriodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate, or acid citrate, tartrate or bitartrate, oxalate, succinate, maleate, gluconate, methanesulfonate, ethanesulfonate, benzenesulfonate and p-toluenesulfonate salts.

As previously indicated, the compounds of the present invention are all readily adapted to therapeutic use as antihypertensive agents in view of their ability to lower the blood pressure of correspondingly agitated subjects. For instance, 2-guanidinomethyl-1,4-benzodioxane has been found to produce a definite antihypertensive effect in man by lowering the blood pressure of hypertensive patients to a statistically significant degree when orally administered to them. Additionally, this particular compound produces its antihypertensive effect in man in both the lying and standing positions, although the effect is more pronounced when the patient is standing. Furthermore, no problems of toxicity or any other untoward side effects have been encountered in the administration of these compounds.

In accordance with a method of treatment of the present invention, the herein described antihypertensives can be administered to an agitated subject via the oral or parenteral routes. In general, these compounds are most desirably administered in doses ranging from about 10 mg. up to about 240 mg. per day, although variations will necessarily occur depending upon the weight of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of from about 0.15 mg. to about 4.8 mg. per kg. of body weight per day is most desirably employed in order to achieve effective results. Nevertheless, it is to be appreciated that still other variations may also occur in this respect, depending upon the species of animal being treated and its individual response to said medicament, as well as on the particular type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger dosages may be employed without causing any harmful or deleterious side effects to occur provided that such higher dose levels are first divided into several smaller doses that are to be administered throughout the day.

In connection with the use of the 2-guanidinoalkyl-1,4-benzodioxane compounds of this invention for the treatment of agitated subjects, it is to be noted that they may be administered either alone or in combination with pharmaceutically acceptable carriers by either of the routes previously indicated, and that such administration can be carried out in both single and multiple dosages. More particularly, the novel compounds of this invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, aqueous suspensions, injectable solution, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic solvents, etc. Moreover, such oral pharmaceutical compositions can be suitably sweetened and/or flavored by means of various agents of the type commonly employed for just such a purpose. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging from about 0.5% to about 90% by weight of the total composition, i.e., in amounts which are sufficient to provide the desired unit dosage previously indicated.

For purposes of oral administration, tablets containing various excipients such as sodium citrate, calcium carbonate and dicalcium phosphate may be employed along with various disintegrants such as starch and preferably potato or tapioca starch, alginic acid and certain complex silicates, together with binding agents such as polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such a magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in soft and hard-filled gelatin capsules; preferred materials in this connection would also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are desired for oral administration, the essential active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes and, if so desired, emulsifying and/or suspending agents, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

For purposes of parenteral administration, solutions of these particular 2 - guanidinoalkyl - 1,4 - benzodioxanes in sesame or peanut oil or in aqueous-propylene glycol or N,N-dimethylformamide may be employed, as well as sterile aqueous solutions of the corresponding water-soluble, non-toxic mineral and organic acid addition salts previously enumerated. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. These particular aqueous solutions are especially suitable for intravenous, intramuscular and intraperitoneal injection purposes. In this connection, the sterile aqueous media employed are readily obtained by standard techniques well-known to those in the art. For instance, dis-

tilled water is ordinarily used as the liquid diluent and the final preparation is passed through a suitable bacterial filter, such as a sintered-glass filter or a diatomaceous-earth or unglazed porcelain filter. Preferred filters of this type include the Berkefeld, the Chamberland and the asbestos disc-metal Seitz filter, wherein the fluid is sucked through the filter candle into a sterile container with the aid of a suction pump. Needless to say, the necessary steps should be taken throughout the preparation of these injectable solutions to ensure that the final products are obtained in a sterile condition.

This invention is further illustrated by the following examples, which are not to be construed in any way as imposing limitations upon the scope thereof. On the contrary, it is to be clearly understood that resort may be had to various other embodiments, modifications and equivalents thereof which readily suggest themselves to those skilled in the art without departing from the spirit of the present invention and/or the scope of the appended claims. In these examples, parts by weight bear the same relation to parts by volume as grams do to milliliters. Further, the percentage values expressed herein are always by weight except where otherwise stated.

Example I

Three and one-third parts by weight of 2-aminomethyl-1,4-benzodioxane and 2.78 parts by weight of S-methyl isothiouronium sulfate were dissolved in 20 parts by volume of water, and the resulting aqueous solution was heated under reflux for three hours. At the end of this time, the solvent was removed by means of evaporation under reduced pressure and the residue so obtained dissolved in a minimum amount of fresh water and treated with charcoal. Upon filtration, there was obtained a clear filtrate which, on standing, soon afforded pure crystals of di(2-guanidinomethyl-1,4-benzodioxane) sulfate, M.P. 204–205° C.

Anal.—Calcd. for $C_{20}H_{28}N_6O_8S$: C, 46.87; H, 5:51; S, 6.26. Found: C, 46.88; H, 5.75; S, 6.40.

Example II

Three and two-tenths parts by weight of 2-aminoethyl-1,4-benzodioxane and 2.5 parts by weight of S-methyl isothiouronium sulfate were dissolved in 10 ml. of water, and the resulting aqueous solution was heated under reflux for four hours. Upon cooling, the solid material which had started to separate during the course of the reaction was removed by means of suction filtration and recrystallized once from aqueous ethanol and then from water. In this manner, there was obtain di[2-(2-guanidinoethyl)-1,4-benzodioxane] sulfate, M.P. 250–252° C.

Anal.—Calcd. for $C_{22}H_{32}N_6O_8S$: C, 48.87; H, 5.97; N, 15.55; S, 5.93. Found: C, 48.62; H, 6.02; N, 15.51; S, 5.73.

Example III

A mixture consisting of 3.0 parts by weight of 2-(3-aminopropyl)-1,4-benzodioxane, 2.2 parts by weight of S-methyl isothiouronium sulfate, and 10 parts by volume of ethanol together with 10 parts by volume of water, was heated on a steam bath for six hours. On standing at room temperature (~25° C.) overnight, i.e., for about 16 hours, the product soon crystallized. It was subsequently removed by means of filtration, crystallized from aqueous ethanol once and then from water twice to give 1.9 parts by weight of pure di[2-(3-guanidinopropyl)-1,4-benzodioxane] sulfate, M.P. 202–205° C. (decomp.).

Anal.—Calcd. for: $C_{24}H_{36}N_6O_8S$: C, 50.7; H, 6.38; N, 14.78. Found: C, 50.6; H, 6.33; N, 14,65.

Example IV

Nine parts by weight of 2-aminomethyl-6,7-dichloro-1,4-benzodioxane and 5.35 parts by weight of S-methyl isothiouronium sulfate in 30 ml. of aqueous ethanol formed a solution which was subsequently heated under reflux for six hours. Upon cooling, the solid material which had separated during the course of the reaction was removed by means of suction filtration and thereafter twice recrystallized from glacial acetic acid and, finally, from water. In this manner, there was obtained di(2-guanidinomethyl - 6,7-dichloro-1,4-benzodioxane) sulfate, M.P. 281–283° C.

Anal.—Calcd. for $C_{20}H_{24}Cl_4N_6O_8S$: C, 36.94; H, 3.72; N, 12.93; S, 4.93; Cl, 21.80. Found: C, 36.58; H, 3.40; N, 12.99; S, 5.13; Cl, 21.52.

Example V

A mixture consisting of 5.0 parts by weight of 2-aminomethyl-6(7)-methyl-1,4-benzodioxane and 3.8 parts by weight of S-methyl isothiouronium sulfate in 10 parts by volume of water was made homogenous by the addition of ethanol and thereafter heated on a steam bath for four hours. The resulting solution was then evaporated under reduced pressure on a steam bath and the residue so obtained dried by azeotropic distillation with toluene, followed by extraction with aqueous ethanol. The ethanolic extract was then concentrated in vacuo and the resulting crystalline material once recrystallized from ethanol, once from aqueous ethanol and then twice from water. In this manner, there were obtained 1.3 parts by weight of di(2-guanidinomethyl - 6(7)-methyl-1,4-benzodioxane) sulfate, M.P. 215–218° C.

Anal.—Calcd. for $C_{22}H_{32}N_6O_8S$: C, 48.90; H, 5.97; N, 15.55. Found: C, 48.60; H, 6.23; N, 15.53.

Example VI

A mixture consisting of 15 parts by weight of 2-aminomethyl - 5(8) - methyl - 1,4 - benzodioxane, 11.6 parts by weight of S-methyl isothiouronium sulfate, 20.20 parts by volume of water and sufficient ethanol to render the mixture homogenous was heated on a steam bath for five hours. The water was then removed from the reaction mixture by means of azeotropic distillation with toluene, and the resulting residual solid was crystallized once from aqueous ethanol and then twice recrystallized from water. In this manner, there were obtained three parts by weight of di(2 - guanidinomethyl-5(8)-methyl-1,4-benzodioxane) sulfate, M.P. 260–262° C. (decomp.).

Anal.—Calcd. for $C_{22}H_{32}N_6O_8S$: C, 48.90; H, 5.97; N, 15.55. Found: C, 48.80; H, 5,82; N, 15.8.

Example VII

A solution consisting of 3.0 parts by weight of 2-aminomethyl-5(8)-isopropyl-1,4-benzodioxane and 2.0 parts by weight of S-methyl isothiouronium sulfate in 15 parts by volume of water with sufficient ethanol to make the mixture homogeneous was refluxed for six hours. The solvent was then removed in vacuo on a steam bath, and the resulting product dried by means of azeotropic distillation with toluene. The syrup which resulted was eventually partially solidified after prolonged trituration with diethyl ether. Recrystallization from water then gave 0.1 part by weight of di(2-guanidinomethyl-5(8)-isopropyl-1,4-benzodioxane) sulfate, M.P. 190° C.

Anal.—Calcd. for $C_{26}H_{40}N_6O_8S$: C, 52.30; H, 6.76; N, 14.08. Found: C, 52.50; H, 6.62; N, 13.78.

Example VIII

A mixture of one part by weight of 2-aminomethyl-7-chloro-1,4-benzodioxane and 0.7 part by weight of S-methyl isothiouronium sulfate in aqueous ethanol was heated for 24 hours. The mixture was subsequently evaporated on a steam bath in vacuo and dried by azeotropic distillation with toluene. The syrup which resulted was then boiled in water with charcoal, filtered and cooled to room temperature. On standing, there was obtained 0.12 part by weight of di(2-guanidinomethyl-7-cloro-1,4-benzodioxane) sulfate, M.P. 222–224° C.

Anal.—Calcd. for $C_{20}H_{26}Cl_2N_6O_8S$: C, 41.30; H, 4.51; Cl, 12.20; N, 14.45. Found: C, 41.60; H, 4.21; Cl, 12.04; N, 14.42.

Example IX

A mixture consisting of 4.8 parts by weight of 2-aminomethyl-5(8)-methoxy-1,4-benzodioxane and 3.24 parts by weight of S-methyl isothiouronium sulfate in aqueous ethanol was heated for six hours on a steam bath. The solvent was then removed by means of evaporation under reduced pressure on a steam bath and ethanol was added to the residual oil which eventually solidified. The sticky solid thus obtained was washed twice with boiling ethanol, and then recrystallized twice from aqueous ethanol and once from water. In this manner, there was obtained 0.18 part by weight of di(2-guanidinomethyl-5(8)-methoxy-1,4-benzodioxane) sulfate, M.P. 278–283° C.

Anal.—Calcd. for $C_{22}H_{32}N_6O_{10}S$: C, 46.10; H, 5.63; N, 14.68. Found: C, 46.20; H, 5.78; N, 14.73.

Example X

Ten and nine-tenths parts by weight of 2-aminomethyl-7-methoxy-1,4-benzodioxane in 15 parts by weight of ethanol were heated on a steam bath for 10 hours with 7.78 parts by weight of S-methyl isothiouronium sulfate in 40 parts by volume of water. Upon completion of this step, the resulting aqueous solution was heated with charcoal and then filtered. The filtrate thus obtained deposited a gum on cooling and the latter material eventually solidified. This solid was then recrystallized from water six times and there were obtained 2.32 parts by weight of di(2-guanidinomethyl-7-methoxy-1,4-benzodioxane) sulfate, M.P. 224–227° C.

Anal.—Calcd. for $C_{22}H_{32}N_6O_{10}S$: C, 46.10; H, 5.63; N, 14.68. Found: C, 45.90; H, 5.40; N, 14.53.

Example XI

Nine parts by weight of 2-hydrazinomethyl-1,4-benzodioxane and 7.0 parts by weight of S-methyl isothiouronium sulfate were refluxed together in 25 ml. of water for 1.5 hours. Upon completion of this step, an oil soon precipitated from the reaction mixture while standing at room temperature (~25° C.). This oil eventually crystallized and after several recrystallizations from water, there was obtained di(2-guanidinoaminomethyl-1,4-benzodioxane) sulfate, M.P. 193–195° C.

Anal.—Calcd. for $C_{20}H_{30}N_8O_8S$: C, 44.27; H, 5.57; N, 20.65; S, 5.91. Found: C, 44.08; H, 5.47; N, 20.30; S, 5.55.

Example XII

Six and six-tenths parts by weight of 2-aminomethyl-1,4-benzodioxane and 9.28 parts by weight of N,S-dimethyl isothiouronium hydriodide in 15 ml. of aqueous dimethylformamide were heated on a steam bath for six hours. The solvent was then removed from the reaction mixture by means of distillation and the residual material basified with 10 N sodium hydroxide solution. Upon extraction of the resulting mixture with chloroform followed by a three-fold extraction of the chloroform extract with dilute hydrochloric acid, there was obtained a slightly acidic aqueous solution which was subsequently basified by the addition of excess solid sodium hydroxide. The basified aqueous solution was then extracted with chloroform, and the latter extract subsequently dried over anhydrous magnesium sulfate and filtered. The solvent was then removed from the resulting filtrate by means of distillation and the residue thus obtained was subsequently dissolved in methanol, and thereafter added to a solution of excess l-di-(p-toluoyl)-D-tartaric acid in methanol. The desired salt then precipitated from solution on the addition of diethyl ether, and after recrystallization from absolute ethanol, there was obtained [2-(3-methylguanidino)-methyl-1,4-benzodioxane] l-di-(p-toluoyl)-D-hydrogen tartrate, M.P. 158–160° C. (decomp.).

Anal.—Calcd. for $C_{31}H_{33}N_3O_{10}$: C, 61.28; H, 5.47; N, 6.92. Found: C, 61.51; H, 5.36; N, 6.93.

Example XIII

Three and one-third parts by weight of 2-aminomethyl-1,4-benzodioxane and 4.92 parts by weight of N,N',S-trimethyl isothiouronium hydriodide in 10 ml. of aqueous dimethylformamide were warmed together on a steam bath for six hours. The solvent was then removed from the reaction mixture by means of distillation, and the residual oil basified with 10 N sodium hydroxide solution. The resulting aqueous solution was then extracted with diethylether, and the ether extract thus obtained was subsequently dried over anhydrous magnesium sulfate. Upon removal of the drying agent by means of filtration and the solvent by means of distillation, there was obtained a residual material which was subsequently dissolved in methanol and added to a solution of excess l-di-(p-toluoyl)-D-tartaric acid in the same solvent. The salt which resulted was recovered by means of precipitation with diethylether and filtered from the mixture. After several recrystallizations from methanol, there was obtained [N-methyl-2-(3-methylguanidino)-methyl-1,4-benzodioxane] l-di-(p-toluoyl)-D-hydrogen tartrate, M.P. 146° C. (decomp.).

Anal.—Calcd. for $C_{32}H_{35}N_3O_{10}$; C, 61.83; H, 5.68; N, 6.76. Found: C, 62.05; H, 5.56; N, 6.91.

Example XIV

2-(N-methyl)-aminomethyl - 1,4-benzodioxane (5.37 parts by weight) and S-methyl isothiouronium sulfate (4.18 parts by weight) in 20 ml. of aqueous ethanol were refluxed together for 48 hours. The solvent was then removed by means of distillation under reduced pressure, and the residue so obtained was crystallized from ethanol and then from water. In this manner, there was obtained di[2-(1-methylguanidino)methyl-1,4-benzodioxane] sulfate, M.P. 271–272° C. (decomp.).

Anal.—Calcd. for $C_{22}H_{32}N_6O_8S$: C, 48.87; H, 5.97; N, 15.55; S, 5.93. Found: C, 49.30; H, 5.86; N, 15.22; S, 5.67.

Example XV

2-aminomethyl - 1,4 - benzodioxane (4.13 parts by weight) and S-methyl N,N'-ethyleneisothiouronium hydriodide (6.1 parts by weight) in 25 ml. of absolute ethanol were refluxed together for six hours. The solvent was then removed by means of distillation under reduced pressure, and the residual oil which resulted was dissolved in a small amount of ethanol and basified with 10 N sodium hydroxide solution. The resulting aqueous solution was then extracted with diethylether and the ether extracts subsequently dried over anhydrous potassium carbonate and filtered. The filtrate was then concentrated under reduced pressure and the residual material taken up in a minimum amount of absolute ethanol and added as such to a solution of excess l-di-(p-toluoyl)-D-tartaric acid in ethanol. On standing, a solid material soon precipitated which was filtered and thereafter twice recrystallized from ethanol. In this manner, there was obtained pure [2-(N,N'-ethyleneguanidinomethyl) - 1,4-benzodioxane] l-di-(p-toluoyl)-D-hydrogen tartrate, M.P. 176–177° C. (decomp.).

Anal.—Calcd. for $C_{32}H_{33}N_3O_{10}$; C, 62.03; H, 5.37; N, 6.78. Found: C, 61.78; H, 5.29; N, 6.86.

Example XVI

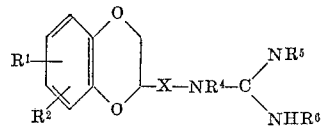
Ten parts by weight of di(2-guanidinomethyl-1,4-benzodioxane) sulfate in 50 parts by volume of water is neutralized with 10 N sodium hydroxide solution. Extraction of the resulting aqueous solution with several portions of methylene chloride, followed by separation of the organic layer and its subsequent concentration under reduced pressure then affords 2-guanidinomethyl-1,4-benzodioxane as a free base.

In like manner, when each of the other 2-guanidinoalkyl-1,4-benzodioxane salt compounds reported in Examples II–XV is subject to this same reaction procedure,

the corresponding free organic base is always the product obtained.

Example XVII

The following 2-guanidinoalkyl-1,4-benzodioxanes can be prepared according to the procedure of the previous examples from the appropriate starting compounds:



R^1	R^2	X	R^4	R^5	R^6
5(8)-Br	H	CH_2	n-C_3H_7	H	H
H	6(7)-Br	C_2H_4NH	H	H	CH_3
6-Br	7-Br	C_3H_6	CH_3	H	iso-C_3H_7
H	H	C_2H_4	C_2H_5	—CH_2—CH_2—	
5(8)-C_2H_5	H	CH_2	iso-C_3H_7	H	C_2H_5
H	6(7)-C_3H_7	C_2H_4	CH_3	H	CH_3
6-CH_3	7-CH_3	C_3H_6	H	H	n-C_3H_7
H	H	CH_2NH	n-C_3H_7	CH_3	CH_3
H	6(7)-C_2H_5	C_3H_6	H	H	H
5(8)-OC_3H_7	H	CH_2	CH_3	C_2H_5	C_2H_5
H	6(7)-OC_2H_5	C_2H_4	C_2H_5	—CH_2—CH_2—	
6-OCH_3	7-OCH_3	C_3H_6	n-C_3H_7	H	H
5(8)-Cl	6(7)-OCH_3	C_2H_4NH	H	H	CH_3
H	H	C_3H_6	n-C_3H_7	H	H
5(8)-C_2H_5	6(7)-Br	CH_2	CH_3	H	H
5(8)-Cl	6(7)-Cl	C_3H_6	H	H	H
H	H	C_3H_6	H	—CH_2—CH_2—	

Example XVIII

The non-toxic hydrohalide acid addition salts of each of the 2-guanidinoalkyl-1,4-benzodioxane bases reported previously in Examples XVI–XVII, such as hydrochloride, hydrobromide and hydriodide salts thereof, are individually prepared by first dissolving the respective organic base compound in absolute ether followed by introduction of the appropriate hydrogen halide gas into the reaction solution until saturation of same is complete with respect to said gas, whereupon the desired salt precipitates from solution. The crystalline product so obtained is then recrystallized from acetone-ether to yield the pure hydrohalide salt. For instance, when 1.0 g. of 2-guanidinomethyl-1,4-benzodioxane is dissolved in anhydrous diethyl ether and dry hydrogen chloride gas is subsequently passed into the resulting solution until saturation of same is complete with respect to said gas, there is obtained a crystalline precipitate of 2-guanidinomethyl-1,4-benzodioxane hydrochloride.

Example XIX

The nitrate, sulfate or bisulfate (other than those previously recorded (phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bitartrate, oxalate, succinate, maleate, gluconate, saccharate, methanesulfonate, ethanesulfonate, benzenesulfonate and p-toluenesulfonate salts of each of the 2-guanidinoalkyl-1,4-benzodioxane bases previously reported in Examples XVI–XVII are all prepared by separately dissolving in a suitable amount of ethanol the proper molar amounts of the respective acid and the appropriate organic base and then mixing the two solutions together, followed by the addition of diethyl ether to the resulting reaction solution in order to effect precipitation of the desired acid addition salt therefrom. For instance, when equimolar amounts of 2-(3-methylguanidino)methyl-1,4-benzodioxane and concentrated sulfuric acid react in accordance with this procedure, the corresponding product obtained is di[2-(3-methylguanidino)methyl-1,4-benzodioxane] sulfate. In like manner, each of the other salts are similarly prepared.

Example XX

A solution of 3.8 g. (0.08 mole) of sodium hydride (50% dispersion in oil) in tert.-butanol (sodium-dried)

was treated with 8.1 g. (0.085 mole) of guanidine hydrochloride in one portion. The mixture was then stirred and refluxed on a steam bath for 30 minutes, filtered while still hot and added to a refluxing solution of 13 g. (0.04 mole) of 2-(p-toluenesulfonyloxy)methyl-1,4-benzodioxane dissolved in 30 ml. of tert.-butanol. The reaction mixture was then stirred and refluxed for seven hours, after which time it was evaporated to dryness under reduced pressure. Upon extraction of the residue with three-25 ml. portions of hot water followed by subsequent cooling of said extracts, there were obtained 9.4 g. of 2-guanidinomethyl-1,4-benzodioxane as the p-toluenesulfonate, M.P. 170–175° C. After several recrystallizations from water or ethanol, the melting point was raised to 178–180° C. (analytical sample).

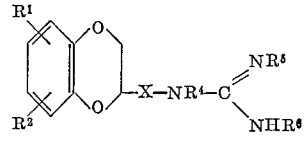
Example XXI

The procedure described in the previous example is repeated employing in place of the p-toluenesulfonate of 2-hydroxymethyl-1,4-benzodioxane as the starting material for this reaction the corresponding salts of any other 2-hydroxyalkyl-1,4-benzodioxanes whose structures correspond in scope to those of the 2-aminoalkyl-1,4-benzodioxanes employed previously as starting materials in Examples II–XV as well as in Example XVII.

What is claimed is:

1. 2-guanidinoaminomethyl-1,4-benzodioxane.

2. A compound selected from the group consisting of organic bases of the formula:



and the pharmaceutically acceptable acid addition salts thereof wherein each of R^1 and R^2 is selected from the group consisting of hydrogen, chlorine, bromine, lower alkyl and lower alkoxy; X is selected from the group consisting of lower alkylene, —CH_2NH— and

—CH_2CH_2NH—

R^4 is selected from the group consisting of hydrogen and lower alkyl and R^5 and R^6, when taken together with the nitrogen atoms to which they are attached and the carbon atom which is geminal to said nitrogen atoms, are imidazolinyl.

3. A compound of claim 2 wherein R^1 and R^2 and R^4 are each hydrogen and X is lower alkylene.

4. 2 - (N,N' - ethyleneguanidinomethyl) - 1,4 - benzodioxane.

No references cited.

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