United States Patent Office

2,876,222

Patented Mar. 3, 1959

2,876,222

1,2,3,4-TETRAHYDROQUINOLYL AND 1,2,3,4-TETRAHYDROISOQUINOLYL DERIVATIVES OF 1,3-DIAZACYCLOHEXENE-2

Barry M. Bloom, Jackson Heights, N. Y., assignor to Chas. Pfizer & Co., Inc., New York, N. Y., a corporation of Delaware

No Drawing. Application October 18, 1956
Serial No. 616,594

10 Claims. (Cl. 260—256.4)

This invention is concerned with new and highly effective therapeutic agents. In particular it is concerned with substituted and unsubstituted 1,2,3,4-tetrahydroquinolyl-1,3 - diazacyclohexene-2, 1,2,3,4 - tetrahydroisoquinolyl-1,3-diazacyclohexene-2 and their pharmaceutically acceptable acid addition salts.

In my copending and concurrently filed patent application Serial No. 616,639, entitled "Therapeutic Agents," I describe certain 1,2,3,4-tetrahydroquinolyl-1,3-diazacyclopentene-2, 1,2,3,4,-tetrahydroisoquinolyl-1,3-diazacyclopentene-2 and their pharmaceutically acceptable acid addition salts. These agents are potent regulators of the cardiovascular system having the special property of functioning as hypotensive agents.

I have now unexpectedly discovered that when the diazacyclopentene ring of the above described therapeutic agents is replaced with a diazacyclohexene ring the resulting products, while still functioning as regulators of the cardiovascular system, have a special property opposite in nature to the 5-membered ring compounds, that is, they are pressor amines.

The term, "pressor amine" has a definite meaning to one skilled in the art. It refers to an organic amine which has the physiological effect of vasoconstriction and other epinephrine like properties. These materials cause constriction of the blood vessel walls thereby decreasing the volume of the blood vessels and increasing the blood pressure. They are used topically to cause constriction of the blood vessels of the nose in treatment of allergic rhinitis, sinusitis, acute coryza and hay fever.

The compounds of the present invention are diazacyclohexenes wherein the number two carbon atom of said diazacyclohexenes is attached to the heterocyclic nitrogen atom of a tetrahydroquinolyl or tetrahydroisoquinolyl ring. Both substituted and unsubstituted compounds of the instant invention are found to possess pressor amine activity. The substituents on a substituted pressor amine may be divided into classes according to whether they are on the aromatic ring of the tetrahydroquinoline or tetrahydroisoquinoline moieties, the partially reduced ring of these moieties or the carbon atoms of the diazacycloalkene ring.

The aromatic ring of the tetrahydroquinoline and tetrahydroisoquinoline moieties may be substituted with halogen atoms, that is, chlorine, bromine and iodine, alkoxy and alkyl groups containing up to four carbon atoms and hydroxyl groups. The substituents on the partially reduced ring include alkyl groups containing up to four carbon atoms.

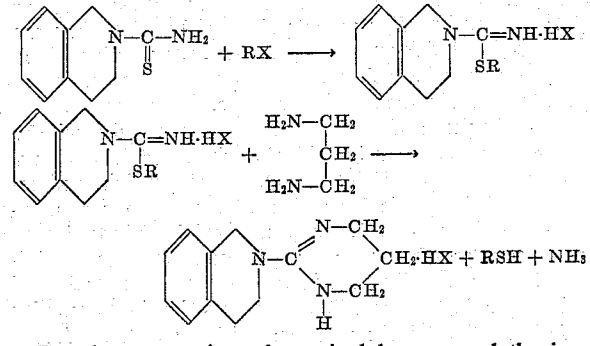
The substituents on the number four and six carbon atoms of the diazacyclohexene ring are alkyl groups containing up to four carbon atoms. In addition to alkyl groups containing up to four carbon atoms, the number five carbon atom of the diazacyclohexene ring may be substituted with a hydroxyl group.

The following list is illustrative of the compounds within the purview of this invention.

(1) 2-(1',2',3',4'-tetrahydro-1'-quinolyl)-1,3 - diazacyclohexene-2.
(2) 2-(1',2',3',4'-tetrahydro-2'-n-butyl - 1'-quinolyl)-1,3-diazacyclohexene-2.
(3) 2-(1',2',3',4'-tetrahydro-6',7'-diethoxy-1'-quinolyl)-1,3-diazacyclohexene-2.
(4) 2-(1',2',3',4'-tetrahydro-6',7'-dihydroxy-1'-quinolyl)-1,3-diazacyclohexene-2.
(5) 2-(1',2',3',4'-tetrahydro-6'- n-propyl-1'- quinolyl)-1,3-diazacyclohexene-2.
(6) 2-(1',2',3',4'-tetrahydro-2'- methyl-1'- quinolyl)-4,5-di-n-propyl-1,3-diazacyclohexene-2.
(7) 2-(1',2',3',4'-tetrahydro-6',7'- dibromo-1'- quinolyl)-4-isopropyl-1,3-diazacyclohexene-2.
(8) 2-(1',2',3',4'-tetrahydro-5'- chloro-1'- quinolyl)-4,5-dimethyl-1,3-diazacyclohexene-2.
(9) 2-(1',2',3',4'- tetrahydro-8'- iodo-1'- quinolyl)-5-hydroxy-1,3-diazacyclohexene-2.
(10) 2-(1',2',3',4'- tetrahydro-2'- isoquinolyl)-1,3 - diazacyclohexene-2.
(11) 2-(1',2',3',4'- tetrahydro-1-methyl - 2'- isoquinolyl)-1,3-diazacyclohexene-2.
(12) 2-(1',2',3',4'-tetrahydro-3'- ethyl-2'- isoquinolyl)-4-ethyl-1,3-diazacyclohexene-2.
(13) 2-(1',2',3',4'-tetrahydro - 6',7'- di - n-butyl - 2'- isoquinolyl)-4,5-di-n-butyl-1,3-diazacyclohexene-2.
(14) 2 - (1',2',3',4' - tetrahydro - 3',4' - diethyl - 2' - isoquinolyl)-4,5-diethyl-1,3-diazacyclohexene-2.
(15) 2-(1',2',3',4'-tetrahydro-8'-bromo-2'-isoquinolyl)-4-methyl-1,3-diazacyclohexene-2.
(16) 2-(1',2',3',4'-tetrahydro-6'-hydroxy-2'- isoquinolyl)-1,3-diazacyclohexene-2.
(17) 2-(1',2',3',4'- tetrahydro-2'- isoquinolyl)-5-hydroxy-1,3-diazacyclohexene-2.
(18) 2-(1',2',3',4'-tetrahydro-2'- isoquinolyl)-4,6-diethyl-1,3-diazacyclohexene-2.

The compounds of my invention are best prepared by the method described in my copending and concurrently filed patent application Serial No. 616,640, entitled "Synthesis of 1,3-diazacycloalkene-2." In that application I describe the synthesis of 1,3-diazacycloalkene-2 by the reaction between an isothiouronium salt and a diaminoalkane. An isothiouronium salt is prepared for example by the reaction between an alkyl or an aralkyl halide or sulfate and an N-naphthyl substituted thiourea. For purposes of the present invention the isothiouronium salt is prepared by the reaction between an alkyl or aralkyl halide or sulfate and an N-thiocarbamido-1,2,3,4-tetrahydroquinoline or N-thiocarbamido-1,2,3,4-tetrahydroisoquinoline, the quinolyl and isoquinolyl rings being substituted or unsubstituted in conformance with the description given above.

The synthesis applied to an isoquinolyl compound of the present invention is illustrated below.



For the preparation of a quinolyl compound the isoquinolyl isothiouronium salt of the above equation would be replaced with a quinolyl isothiouronium salt.

By reference to the above equation it can be seen that the size of the alkyl or aralkyl group, here represented by R, in the halide or sulfate used to form the isothiouronium salt is of no consequence as far as the final structure of the active compounds of my invention is concerned since it is ultimately removed in the form of a mercaptan. It is, however, convenient to use low molecular weight alkyl halides or sulfates such as methyl iodide or dimethyl sulfate since the mercaptans which are ultimately formed from these types of compounds are relatively volatile and easily removed.

The symbol "X" in the above equation refers to a chloride, bromide, iodide or sulfate ion which together with the active cation forms a pharmaceutically acceptable acid addition salt. Other pharmaceutically acceptable acid addition salts such as, for example, succinate, maleate, tartrate, citrate and glycolate can be formed from the halides or sulfates. They can be formed, for example, by converting the halide or sulfate to the free base and treating the free base with the chosen acid in aqueous solution. Other methods of obtaining these valuable pharmaceutically acceptable acid addition salts are known to those skilled in the art.

The diaminoalkanes of the above reaction include diaminoalkanes such as 1,3-diaminopropane and alkyl substituted derivatives wherein the alkyl group and/or groups which replace the hydrogen and/or hydrogens on various carbon atoms contain up to four carbon atoms. Also included are the above 1,3-diaminopropanes in which the carbon atom between the two carbon atoms which carry amino groups is substituted with a hydroxyl group. Compounds of this latter type give rise to 5-hydroxy-substituted 1,3-diazacyclohexenes-2.

The acid addition salt which is obtained by carrying out the reactions illustrated in the equations given above is converted to the free base by dissolving it in water and neutralizing the acid with a suitable alkaline reagent such as sodium carbonate. The base can be isolated from the water by extraction with an immiscible organic solvent preferably one of low volatility such as methylene chloride or benzene.

More specific directions for the preparation of these valuable compounds can be obtained by reference to the appended examples or by reference to the aforesaid patent application, "Synthesis of 1,3-diazacycloalkene-2."

The compounds of this invention may be administered alone but are generally administered as a composition with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets containing such excipients as starch, milk sugar, certain types of clay, etc. They may be administered in capsules either alone or in admixture with the same or equivalent excipients. They may also be administered orally in the form of elixirs or oral suspensions which may contain flavoring or coloring agents. They may be injected parenterally, that is, for example, intramuscularly or subcutaneously. For parenteral admisistration they are best used in the form of a sterile aqueous solution which may contain other solutes, for example, enough saline or glucose to make the solution isotonic.

The physician will determine the dosage which will be most suitable for an individual patient and it will vary with the form of administration, the age, weight and response of the particular patient. Dosage units containing from 0.1 mg. to 100 mg. are useful. Those dosage unit forms which are prepared for subcutaneous administration will usually contain the lowest concentration of the active ingredient. Dosage forms for intramuscular administration will be somewhat higher and those dosage forms intended for oral administration, for example, elixirs, tablets or capsules will contain still more of the active ingredient.

As might be expected, certain of these compounds are more active than others. For example, better activity is found if substituted alkyl groups which are present are no larger than ethyl or are a combination of ethyl and methyl groups with the majority of them being methyl groups. With alkoxy groups better activity is found if there are no more than two carbon atoms attached to the oxygen. It is better to have no more than two hydroxyl groups on a quinolyl or isoquinolyl group and the preferred halogen substituents are chlorine and bromine with no more than three chlorine atoms or two bromine atoms on any given compound.

As noted above the compositions of this invention may take a variety of forms. Various diluents may be employed and the percentage of active ingredient may be varied. It is necessary that the active ingredient constitute a proportion of the composition such that a suitable dosage form will be obtained. Obviously several dosage unit forms may be administered at about the same time. Although compositions with less than 0.05% by weight of active ingredients are suitable, it is preferred to use compositions containing at least 0.05% of the active agent. Activity increases with the concentration of the active agent. The percentage by weight of active agent may be 10, 50, 75, 90% or even higher. Dosage unit forms may be prepared with a minor proportion of a carrier and a major proportion of active materials.

The following examples are given solely for the purpose of illustration and are not to be construed as limitations of this invention, many variations of which are possible without departing from the spirit or scope thereof.

EXAMPLE I

2 - (1',2',3',4' - tetrahydro - 1' - quinolyl) - 1,3 - diazacyclohexene-2

N-thiocarbamido-1,2,3,4-tetrahydroquinoline (50 g.) and 20 ml. of methyl iodide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE II

2 - (1',2',3',4' - tetrahydro - 1' - quinolyl) - 4(or 6)-methyl-1,3-diazacyclohexene-2

N-thiocarbamido-1,2,3,4-tetrahydroquinoline (50 g.) and 20 ml. of methyl iodide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminobutane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE III

2 - (1',2',3',4' - tetrahydro - 6',7' - dimethoxy - 2' - isoquinolyl)-1,3-diazacyclohexene-2

N - thiocarbamido - 6,7 - dimethoxy - 1,2,3,4 - tetrahydroisoquinoline (50 g.) and 20 ml. of methyl bromide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium

salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE IV

2 - (1',2',3',4' - tetrahydro - 2' - isoquinolyl) - 1,3 - diazacyclohexene-2

N-thiocarbamido-1,2,3,4-tetrahydroisoquinoline (50 g.) and 20 ml. of methyl bromide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE V

2 - (1',2',3',4' - tetrahydro - 6' - chloro - 1' - quinolyl)-1,3-diazacyclohexene-2

N - thiocarbamido - 6 - chloro - 1,2,3,4 - tetrahydroquinoline (50 g.) and 20 ml. of dimethyl sulfate are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE VI

2 - (1',2',3',4' - tetrahydro - 6' - methoxy - 1' - quinolyl)-1,3-diazacyclohexene-2

N - thiocarbamido - 6 - methoxy - 1,2,3,4 - tetrahydroquinoline (50 g.) and 20 ml. of benzyl bromide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE VII

2 - (1',2',3',4' - tetrahydro - 6' - chloro - 2' - isoquinolyl)-1,3-diazacyclohexene-2

N - thiocarbamido - 6 - chloro - 1,2,3,4 - tetrahydroisoquinoline (50 g.) and 20 ml. of methyl iodide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE VIII

2 - (1',2',3',4' - tetrahydro - 6' - methoxy - 2' - isoquinolyl) - 1,3 - diazacyclohexene - 2

N - thiocarbamido - 6 - methoxy - 1,2,3,4 - tetrahydroisoquinoline (50 g.) and 20 ml. of methyl iodide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE IX

2 - (1',2',3',4' - tetrahydro - 1' - quinolyl) - 5 - hydroxy-1,3-diazacyclohexene-2

N - thiocarbamido - 1,2,3,4 - tetrahydroquinoline (50 g.) and 20 ml. of methyl iodide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diamino-2-hydroxy propane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE X

2 - (1',2',3',4' - tetrahydro - 6',7' - diethyl - 1' - quinolyl)-1,3-diazacyclohexene-2

N - thiocarbamido - 6,7 - diethyl - 1,2,3,4 - tetrahydroquinoline (50 g.) and 20 ml. of methyl iodide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE XI

2 - (1', 2',3',4' - tetrahydro - 5',8' - dibromo - 1' - quinolyl)-1,3-diazacyclohene-2

N - thiocarbamido - 5,8 - dibromo - 1,2,3,4 - tetrahydroquinoline (50 g.) and 20 ml. of methyl iodide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The sol-

vent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE XII

2 - (1',2',3',4' - tetrahydro - 6', 7' - dichloro - 2' - isoquinolyl)-1,3-diazacyclohexene-2

N - thiocarbamido - 6,7' - dichloro - 1,2,3,4 - tetrahydroisoquinoline (50 g.) and 20 ml. of methyl iodide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE XIII

2 - (1',2',3',4' - tetrahydro - 1' - quinolyl) - 4,5,6 - triethyl-1,3-diazacyclohexene-2

N - thiocarbamido - 1,2,3,4 - tetrahydroquinoline (50 g.) and 20 ml. of benzyl chloride are reflexed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 4-ethyl-3,5-diaminoheptane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE XIV

2 - (1',2',3',4' - tetrahydro - 2',3' - dimethyl - 1' - quinolyl)-1,3-diazacyclohexene-2

N - thiocarbamido - 2,3 - dimethyl - 1,2,3,4-tetrahydroquinoline (50 g.) and 20 ml. of methyl iodide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE XV

2-(1',2',3',4'-tetrahydro-3'-ethyl-2'-isoquinolyl)-1,3-diazacyclohexene-2

N-thiocarbamido-3-ethyl-1,2,3,4-tetrahydroisoquinoline (50 g.) and 20 ml. of n-butyl bromide are refluxed in 200 ml. of methanol for one hour. The solution is cooled and most of the solvent removed in vacuo to give a heavy precipitate of the isothiouronium salt which is recovered by filtration. The salt is taken up in an equimolar methanol solution of 1,3-diaminopropane and heated under reflux for ten hours. The solvent is partially removed in vacuo and the acid addition salt recovered by filtration.

The free base is obtained by treating an aqueous solution of the acid addition salt with aqueous potassium carbonate, extracting the aqueous solution with benzene and removing the organic solvent in vacuo.

EXAMPLE XVI

2-(1',2',3',4'-tetrahydro-2'-ethyl-isoquinolyl)-1,3-diazacyclohexene-2-glycolate

A benzene solution (50 ml.) containing 2.4 g. of 2-(1',2',3',4'-tetrahydro-2'-ethyl-isoquinolyl)-1,3-diazacyclohexene-2 is shaken with 50 ml. of an aqueous solution containing 7.6 g. of glycolic acid. The layers are separated and the glycolic acid salt of 2-(1',2',3',4'-tetrahydro-2'-ethyl-isoquinolyl)-1,3-diazacyclohexene-2 is recovered from the aqueous layer by evaporation of the solvent in vacuo.

Other pharmaceutically acceptable acid addition salts are prepared from the free bases of this invention in an identical manner.

EXAMPLE XVII

A tablet base is prepared by blending the following ingredients in the proportion by weight indicated.

Sucrose U. S. P	82.0
Tapioca starch	13.6
Magnesium stearate	4.4

Into this tablet there is blended a sufficient amount of 2-(1',2',3',4'-tetrahydro-6',7' - dimethoxy-2'-isoquinolyl)-1,3-diazacyclohexene-2 to provide tablets each containing 50 mg. of active ingredient.

EXAMPLE XVIII

Into the table base of Example XVII there is blended a sufficient amount of the hydro-iodide salt of 2-(1',2',3',4'-tetrahydro-6'-chloro-1'-quinolyl) - 1,3-diazacyclohexene-2 to provide tablets each containing 0.5 mg. of active ingredient.

EXAMPLE XIX

A tablet base is prepared by blending the following ingredients in the proportion by weight indicated.

Sucrose U. S. P	80.3
Tapioca starch	13.2
Magnesium stearate	6.5

Into this base there is blended a sufficient amount of 2-(1',2',3',4'-tetrahydro - 6'-methoxy-1'-quinolyl)-1,3-diazacyclohexene-2 to provide tablets each containing 75 mg. of active ingredient.

EXAMPLE XX

Into the tablet base of Example XIX there is blended a sufficient amount of the hydrobromide salt of 2-(1',2',3',4'-tetrahydro - 6'-chloro - 2'-isoquinolyl)-1,3 - diazacyclohexene-2 to provide tablets each containing 0.1 mg. of active ingredient.

EXAMPLE XXI

Ten liters of distilled water for injection, U. S. P. are poured into a 20 l. Pyrex glass bottle. To this water is added sufficient 2-(1',2',3',4'-tetrahydro-6'-methoxy-2'-isoquinolyl)-1,3-diazacyclohexene-2 hydrobromide to provide a 0.1 percent solution by weight.

EXAMPLE XXII

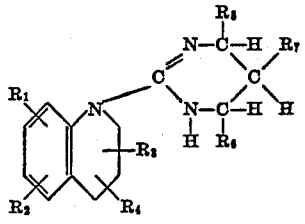
A blend is prepared containing the following ingredients:

	Grams
Calcium carbonate U. S. P.	17.60
Dicalcium sulfate	18.80
Magnesium trisilicate U. S. P.	5.20
Lactose U. S. P.	5.20
Potato starch	5.20
2-(1',2',3',4'-tetrahydro - 1'-quinolyl) - 1,3 - diazacyclohexene-2	4.00
Magnesium stearate A	0.80
Magnesium stearate B	0.32

This blend is divided and formed into tablets each containing 5 mg. of active ingredient.

What is claimed is:

1. A compound selected from the group consisting of



and the pharmaceutically acceptable acid addition salts thereof wherein R_1 and R_2 are each selected from the group consisting of hydrogen, chloro, bromo, iodo, hydroxy and alkyl and alkoxy containing up to 4 carbon atoms; R_3, R_4, R_5 and R_6 are each selected from the group consisting of hydrogen and alkyl containing up to 4 carbon atoms; and R_7 is selected from the group consisting of hydrogen, hydroxy and alkyl containing up to 4 carbon atoms.

2. 2-(1',2',3',4'-tetrahydro - 1'-quinolyl) - 1,3 - diazacyclohexene-2.

3. 2-(1',2',3',4'-tetrahydro - 2'-isoquinolyl) - 1,3-diazacyclohexene-2.

4. 2-(1',2',3',4'-tetrahydro-chloro - 2'-isoquinolyl)-1,3-diazacyclohexene-2.

5. 2-(1',2',3',4'-tetrahydro - 6'-chloro - 2'-isoquinolyl)-1,3-diazacyclohexene-2.

6. 2-(1',2',3',4'-tetrahydro-alkoxy - 2'-isoquinolyl)-1,3-diazacyclohexene-2 wherein the alkoxy group contains up to four carbon atoms.

7. 2-(1',2',3',4'-tetrahydro-6'-methoxy -2'-isoquinolyl)-1,3-diazacyclohexene-2.

8. 2-(1',2',3',4' - tetrahydro - 6',7' - dimethoxy - 2'-isoquinolyl)-1,3-diazacyclohexene-2.

9. 2-(1',2',3',4' - tetrahydro - bromo - 2' - isoquinolyl)-1,3-diazacyclohexene-2.

10. 2-(1',2',3',4'-tetrahydro - iodo - 2'-isoquinolyl)-1,3-diazacyclohexene-2.

References Cited in the file of this patent

Urech et al.: Helvetica Chimica Acta, vol. 33, No. 182, pp. 1386–1407.

Richter's Organic Chemistry, volume IV, pp. 4–7 (1947).

UNITED STATES PATENT OFFICE

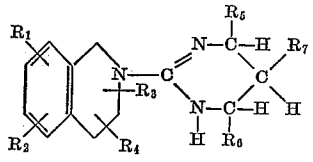
Certificate of Correction

Patent No. 2,876,222 March 3, 1959

Barry M. Bloom

It is hereby certified that error appears in the printed specification of the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 9, claim 1, after the formula appearing between lines 20 and 29, insert the following additional formula:



Signed and sealed this 21st day of July 1959.

[SEAL]

Attest:
KARL H. AXLINE,
Attesting Officer.

ROBERT C. WATSON,
Commissioner of Patents.