United States Patent Office

3,663,706

Patented May 16, 1972

3,663,706

USE OF 2,4-DIAMINOQUINAZOLINES AS HYPOTENSIVE AGENTS

Hans-Jurgen E. Hess, Groton, Conn., assignor to Pfizer Inc., New York, N.Y.

No Drawing. Application Dec. 13, 1967, Ser. No. 690,101, now Patent No. 3,511,836, dated May 12, 1970, which is a continuation-in-part of application Ser. No. 555,704, June 7, 1966, which in turn is a continuation-in-part of application Ser. No. 469,879, Aug. 6, 1965. Divided and this application Sept. 29, 1969, Ser. No. 871,171

Int. Cl. A61k *27/00*

U.S. Cl. 424—251 11 Claims

ABSTRACT OF THE DISCLOSURE

Novel 2,4-diaminoquinazolines wherein at least one of the 6- or 7-positions is substituted with alkoxy having from 1 to 3 carbon atoms and acid addition salts thereof, the preparation thereof and the utility thereof as hypotensive agents.

CROSS REFERENCE TO RELATED APPLICATIONS

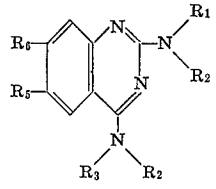
This application is a division of application Ser. No. 690,101 filed Dec. 13, 1967, now U.S. Pat. 3,511,836 which, in turn, is a continuation-in-part of application Ser. No. 555,704 filed June 7, 1966 and now abandoned which, in turn, is a continuation-in-part of application Ser. No. 469,879 filed Aug. 6, 1965 and now abandoned.

BACKGROUND OF THE INVENTION

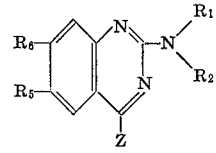
This invention relates to new and useful compounds which are valuable therapeutic agents. More particularly, it is the object of this invention to provide new and useful chemotherapeutic agents valuable in reducing blood pressure in hypertensive subjects.

SUMMARY OF THE INVENTION

In accordance with the present invention, compounds found to have valuable hypotensive properties are those of the formulae:



I



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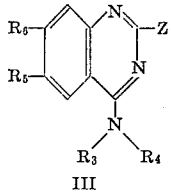
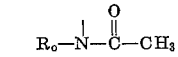


III

where:

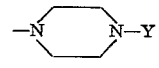
R_1, R_2, R_3 and R_4 are each selected from hydrogen, alkyl having from 1 to 5 carbon atoms, alkenyl having from 3 to 5 carbon atoms, hydroxyalkyl having from 2 to 5 carbon atoms, phenyl, benzyl, phenylethyl, 2-furfuryl and cycloalkyl where alkyl has from 3 to 8 carbon atoms;

Z is selected from morpholino, 1-azacycloheptyl, 1-azacyclooctyl and acetylamino of the formula:



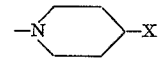
where R_o is hydrogen, acetyl, alkyl having from 1 to 5 carbon atoms and alkenyl having from 3 to 5 carbon atoms; and

piperazino of the formula:



where Y is hydrogen, alkyl having from 1 to 5 carbon atoms, hydroxyalkyl where alkyl has from 2 to 5 carbon atoms, alkanoyl having from 2 to 7 carbon atoms, allyl, propargyl, 2-methylallyl, phenyl, benzyl, benzoyl, halobenzoyl and halophenyl where halo is chloro or bromo, trifluoromethyl, methoxyphenyl, methylphenyl, methylbenzoyl, trifluoromethylbenzoyl, furoyl, benzofuroyl, thenoyl, pyridinecarbonyl, 3,4,5 - trimethoxybenzoyl, carboxylic acid alkyl ester where alkyl has from 1 to 6 carbon atoms, carboxylic acid alkenyl ester where alkenyl has from 3 to 6 carbon atoms; and

piperidino of the formula:



where X is hydrogen, alkyl having from 1 to 5 carbon atoms, alkoxy having from 1 to 4 carbon atoms, hydroxy, hydroxyalkyl where alkyl has from 2 to 5 carbon atoms, phenyl, benzyl, 4-phenyl-4-carboxylic acid alkyl ester where alkyl has from 1 to 6 carbon atoms;

R_5 and R_6 are each selected from hydrogen and alkoxy having from 1 to 3 carbon atoms, at least one of R_5 and R_6 being alkoxy; and the acid addition salts thereof.

Included in the compounds of this invention are

2-dimethylamino-4-amino-6,7-dimethoxyquinazoline,
2-[4-(2-furoyl)-1-piperazine-1-yl]-4-amino-6,7-dimethoxyquinazoline,
2-(4-allyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline,
2-[4-(2-methylallyl)-1-piperazinyl]-4-amino-6,7-dimethoxyquinazoline, and
2-(4-benzoyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline.

Of the preceding compounds, 2-dimethylamino-4-amino-6,7-dimethoxyquinazoline dihydrochloride has been tested and reported by J. D. Thayer et al. in Antibiotics and Chemotherapy, vol. II, No. 9, September 1952, p. 463–466, as an antibacterial agent and found to have a slight order of activity. Furthermore, U.S. Pat. No. 2,945,859, issued on July 19, 1960, to George H. Hitchings et al., discloses 2,4-diamino - 6,7 - dimethylquinazoline as an antibacterial agent. However, it is the existence of these compounds in the aforesaid prior art which necessitates my excluding them and their isomers and homologues, from the compound claims of this invention.

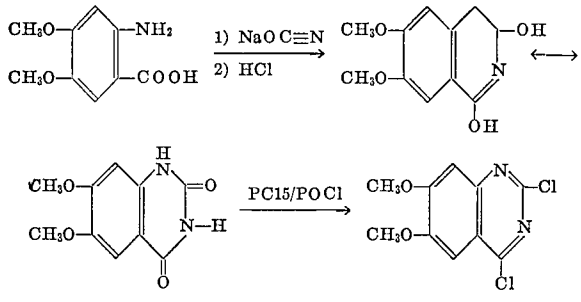
I have also discovered that another group of known compounds have valuable hypotensive activity. These compounds have the structure of Formula I where R_1 and R_3 are hydrogen or alkyl having from 1 to 3 carbon atoms; R_2 and R_4 are hydrogen, alkyl having from 1 to 3 carbon atoms, at least one of R_2 and R_4 is dimethylaminoalkyl, diethylaminoalkyl, dipropylaminoalkyl, methylaminoalkyl, ethylaminoalkyl or propylaminoalkyl where alkyl has from 2 to 4 carbon atoms. Homologues and positional isomers of these compounds are disclosed by Chapman, Gibson and Mann, J. Chem. Soc., 895–898 (1947), and Curd, Hoggarth, Landquist and Rose, J. Chem. Soc., 1766–1773 (1948).

DETAILED DESCRIPTION OF THE INVENTION

The compounds of this invention are particularly effective in reducing blood pressure in hypertensive subjects. On tests with renal hypertensive dogs, as little as 0.06 mg. of active ingredient per kilogram of body weight

was found effective in reducing blood pressure from 180/100 to 160/100 mm. Hg. The results of these tests are shown in the examples below. These compounds are prepared by the cyclization of ureido derivatives of various aromatic acids, amides, nitriles and esters with aqueout base or acid. The ureido derivatives are obtained by reacting the aromatic compound with sodium or potassium cyanate or by reacting the aromatic acid with urea according to the procedure of F.H.S. Curd, et al in the Journal of the Chemical Society (London) 1947, p. 777.

After cyclization, the resulting 2,4-dihydroxyquinazoline is chlorinated at the 2 and 4 positions with a mixture of phosphorus pentachloride and phosphoryl chloride or with a mixture of phosphoryl chloride in N,N'-dimethylaniline. The preparation of 2,4-dichloro-6,7-dimethoxyquinazoline from 4,5-dimethoxyanthranilic acid is shown in the following sequence:



The substituents at the 5,6,7- and 8 positions of quinazoline are controlled to a great extent by the substituents on the starting aromatic acid, amide, nitrile, or ester. Exceptions such as preparing a 5-aminoquinazoline by reducing 5-nitroquinazoline prepared from 6-nitroanthranilic acid are obvious to one skilled in the art. Typical 2,4-dichloroquinazolines, obtained by cyclization and chlorination, and their starting compounds are given in Table I.

TABLE I

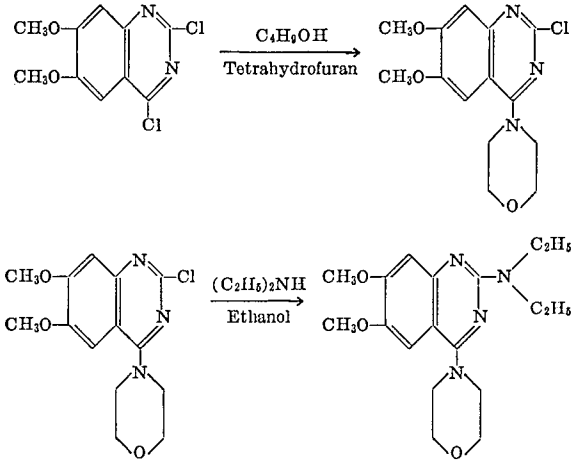
Substituted 2,4-dichloroquinazolines

Starting compounds:	Substituent
5-methoxyanthranilic acid	6-methoxy-
4-methoxyanthranilamide	7-methoxy-
methyl 4-methoxyanthranilate	7-methoxy-
4-methoxyanthranilic acid	7-methoxy-
4-amyloxyanthranilic acid	7-amyloxy-
5-amyloxyanthranilic acid	6-amloxy-
6-aminoveratric acid	6,7-dimethoxy-
4,5-diamyloxyanthranilic acid	6,7-diamyloxy-
5-methylanthranilic acid	6-methyl-
4-methylanthranilic acid	7-methyl-
4-ethylanthranilic acid	7-ethyl-
4-n-propylanthranilic acid	7-n-propyl-
4-isopropylanthranilic acid	7-isopropyl-
5-n-proplanthranilic acid	6-n-propyl-
4,5-dimethylanthranilic acid	6,7-dimethyl-
4,5-di-n-propylanthranilic acid	6,7-di-n-propyl-

The process employed for preparing the novel compounds of this invention involves treating the corresponding 2,4-dichloroquinazoline with the appropriate amine base. The 2-chloro-4-aminoquinazolines are prepared by reacting equimolar quantities of ammonia in tetrahydrofuran and 2,4-dichloroquinazoline. However, in ordinary practice a preferred excess of ammonia would be from one to ten moles in order to shift the reaction to completion. Higher amines and nitrogenous heterocyclic compounds are likewise reacted with the dichloro compound to yield 2-chloro-4-substituted-quinazolines. The temperature at which this reaction can be conducted varies from 25 to about 200° C. for a period of from one to 48 hours. A preferred reaction temperature and time for this reaction would be about 25–60° C. for about four

hours. Upon completion of reaction the product is recovered by conventional means. For instance, the solvent can be evaporated and the crude solid can be triturated with water or precipitated from dilute aqueous acid in crystalline form and subsequently recrystallized from any number of appropriate organic solvents such as methanol or dimethylformamide.

Replacement of chlorine in the 2-position of the quinazoline nucleus is accomplished by reaction of the 2-chloro-4-aminoquinazoline or 2-chloro-4-substituted quinazoline with an amino compound such as piperidine in an aqueous or an organic solvent. A molar excess of base is generally employed, while preferred organic solvents for these purposes include polar solvents like tetrahydrofuran, dioxane, dimethylacetamide, dimethylformamide, or alcohols such as methanol, ethanol, and isoamyl alcohol. The reaction mixture is heated from 100 to 160° C. for from 1 to 65 hours in a sealed pressure bottle. A preferred time and temperature is 140° C. and 4 hours for an alkylamine or heterocyclic compound and 160° C. for 65 hours for ammonia in ethanol. After the reaction is complete, the solvent is evaporated and the product is recrystallized from a mixture of an organic solvent and water. For instance, methanol/water. The reaction is illustrated by the following steps:



The well known procedures for preparing salts of basic compounds are also applicable for the compounds of this invention and are illustrated in the examples below. Such salts may be formed with both pharmaceutically-acceptable and pharmaceutically-unacceptable acids. By "pharmaceutically-acceptable" is meant those salt-forming acids which do not substantially increase the toxicity of the basic compound. The preferred salts are the acid addition salts. These salts are of particular value in therapy. They include salts of mineral acids such as hydrochloric, hydriodic, hydrobromic, phosphoric, metaphosphoric, nitric, and sulfuric acids, as well as salts of organic acids such as tartaric, acetic, citric, malic, benzoic, glycollic, gluconic, gulonic, succinic, arylsulfonic, e.g., para-toluenesulfonic acids, and the like.

The pharmaceutically-unacceptable acid addition salts, while not useful for therapy, are valuable for isolation and purification of the newly recognized biologically-active compounds. Furthermore, they are useful for the preparation of the pharmaceutically-acceptable salts. Of this group, the more common salts include those formed with hydrofluoric and perchloric acids. Hydrofluoride salts are particularly useful for the preparation of the pharmaceutically-acceptable salts, e.g., the hydrochloride, by solution in hydrochloric acid and crystallization of the hydrochloride salt formed. The perchloric acid salts are useful for purification and crystallization of the new compounds.

While the procedures described above are preferred for preparing the compounds of this invention on the

basis of improved yields, alternate methods may also be used. The alternate methods may be divided into eight groups for convenience:

(1) Halogenation of a substituted -3(4)-dihydroquinazoline-4-one to yield substituted-4-haloquinazolines, followed by reaction with a nitrogen-containing compound at position 4.

(2) Thiolation of a substituted -(1H,3H)-quinazoline-2,4-dione with or without subsequent alkylation and reaction with a nitrogen-containing compound.

(3) Alkylation, alkanoylation, aroylation and alkoxylation of piperazine attached to position 2 or 4 of the quinazoline nucleus.

(4) Reaction of guanidine with 2-amino-4,5-dissubstituted benzonitriles to form substituted quinazolines.

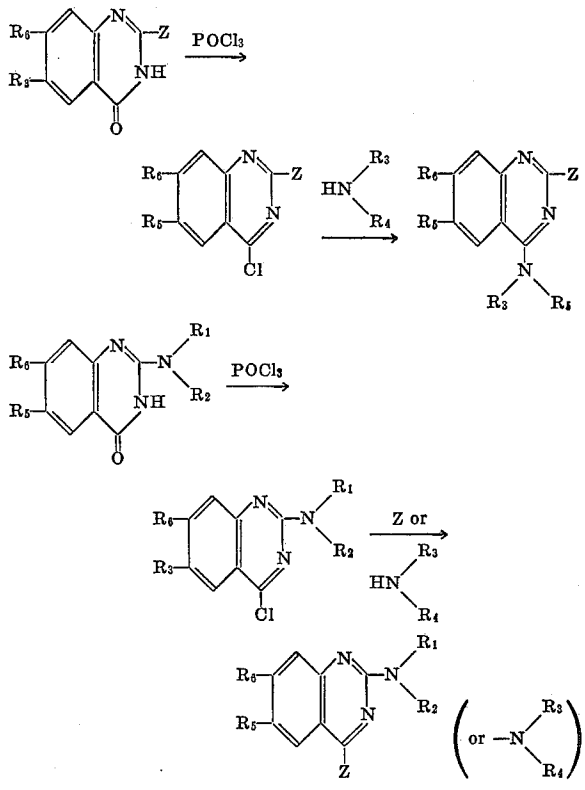
(5) Reaction of guanidines with 2-chloro-4,5-disubstituted-benzonitriles to form 2-substituted amino-4-amino-6,7-disubstituted-quinazolines.

(6) Reaction of guanidines with 2-amidino-4,5-disubstituted-anilines to form 2-substituted-amino-4-amino-6,7-disubstituted-quinazolines.

(7) Reaction of 2-chloro-4-alkoxy-6,7-disubstituted-quinazolines with ammonia or amino compounds to form 2-substituted - amino - 4 - amino-6,7-disubstituted-quinazolines.

(8) Reaction of 2-chloro-4-methylthio - 6,7- - disubstituted-quinazolines with ammonia or amino compounds to form 2-substituted - amino - 4 - amino-6,7-disubstituted-quinazolines.

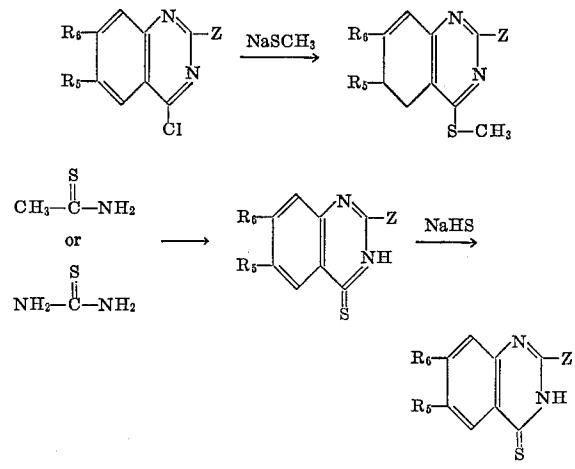
In method (1),4(3H)-quinazolines which are described in previously copending application Ser. No. 442,205 filed Mar. 23, 1965 now abandoned, are halogenated with reagents such as phosphorous oxychloride, phosphorous oxybromide, phosphorus trichloride, phosphorous pentachloride, thionyl chloride or the like, to produce the corresponding 4-haloquinazoline which is then reacted with an amine or heterocyclic compound according to the procedures previously described herein. The following sequence illustrates this method:



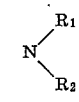
where R_1, R_2, R_3, R_4, R_5, R_6 and Z are as previously described.

In this method, a molar equivalent amount, and preferably an excess, of one of the aforementioned halogenating agents is added to the 3,4-dihydroquinazoline-4-one or an acid salt such as the hydrochloride, sulfate, phosphate, hydrobromide or the like. The reagent is added slowly to the quinazoline at room temperature and then the mixture is refluxed for from about 30 minutes to about 2 hours. The latter time is sufficient for samples of about 10 grams of the quinazoline. Of course, longer reflux periods are desirable for larger batches in order to insure complete reaction. The liquids are evaporated and the resulting crystalline residue is then redissolved in a dilute aqueous solution of sodium bicarbonate, sodium carbonate, sodium hydroxide or the corresponding potassium salts. The aqueous solution is extracted with a solvent such as chloroform or ethyl ether. While the specific extractant is not an essential part of the process, chloroform is preferred on the basis of convenience and safety. The combined extracts are dried with a drying agent such as sodium sulfate, potassium carbonate or the like and the solvent is evaporated to yield the quinazoline substituted with chlorine or bromine on position 4. The resulting compound is reacted with ammonia, amines or heterocyclics by any of the aforementioned methods.

An alternate procedure involving this method, consists in reacting the 4-haloquinazoline with at least a molar equivalent amount of sodium sulfide, thiourea, thioacetamide or sodium methyl mercaptan. Sodium sulfide is reacted from an aqueous solution, sodium methyl mercaptan may be reacted either from aqueous solution or alkanol solution such as methanol, ethanol, isopropanol or the like. Thiourea and thioacetamide are reacted from alkanol solution and ethanol is most convenient. The reaction of the 4-haloquinazoline with these sulfur-containing compounds is accomplished at reflux for from about 2 to 8 hours, depending on the size of the samples. The reactions proceed according to the following:

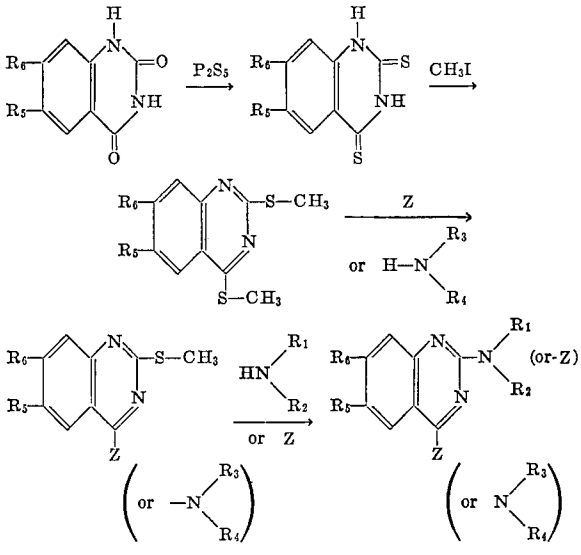


where R_5, R_6 and Z are as previously disclosed and where Z may also be



where R_1 and R_2 are as previously disclosed. The reaction products are allowed to precipitate from the cooled reaction mixture and may be recrystallized from such solvents as ethanol-water mixtures. The recrystallized and dried products may then be reacted with heterocyclics, ammonia or amines according to the procedures previously described for reacting the 4-haloquinazolines to obtain nitrogen substituents on position 4.

In method (2) a substituted quinazoline-2,4-dione is reacted with a reagent such as phosphorous pentasulfide or the like to form the 2,4-dithioquinazoline which in turn is reacted with an alkyl or benzyl halide to form the thioalkyl derivative. The thioalkyl derivative is then reacted with an amine or a heterocyclic compound by the procedures previously described for the reaction of 2,4-dichloroquinazoline to form nitrogen-containing substituents on positions 2 and 4 of the quinazoline nucleus. This method is illustrated by the following sequence:

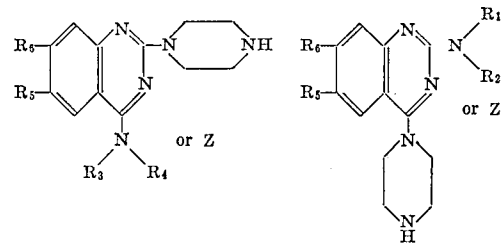


where R_1, R_2, R_3, R_4, R_5, R_6 and Z are as previously described.

The compounds of this invention are prepared by reacting at least a molar equivalent amount of phosphorous pentasulfide with the quinazoline-2,4-dione and preferably an excess of the pentasulfide to ensure complete reaction. While the quinazoline may be dissolved in any non-reactive solvent, the use of a pyridine solution is preferred. The pentasulfide is added to the stirred solution at room temperature and then refluxed with continual stirring. As in the previous method, the reflux time is dependent on the size of the sample. After refluxing, the solvent is removed under reduced pressure, the residue is decomposed with hot water and the solid dithione is filtered from the mixture. To the dithione is added a solvent mixture of aqueous base and an alkanol. Bases useful in this method are sodium hydroxide, potassium hydroxide, and the like. Methanol, ethanol, isopropanol and butyl alcohol are useful in this method and methanol is preferred on the basis of its low boiling point. To the solution is slowly added with stirring at least a twice-molar equivalent of an alkylating agent selected from alkyl iodides, alkyl chlorides, alkyl bromides and the corresponding benzyl halides. On the basis of their ease of removal from their position as alkylmercapto derivatives of quinazoline, methyl and benzyl iodide, are preferred. The mixture is heated to the boiling point of water for about 2 hours. For large samples and for lower temperatures, the time may be extended. The mixture is cooled and the precipitated product is filtered from the mixture. The resulting 2,4-dialkyl- or 2,4-dibenzylmercaptoquinazoline is reacted with ammonia, amines or heterocyclic compounds according to any of the previously described processes for reacting 2,4-dichloroquinazolines, to obtain the compounds of this invention.

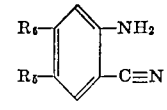
These compounds may also be prepared by reacting the dithione directly with ammonia, amines or a heterocyclic nitrogen compound and equivalent yields of product are obtained thereby.

In method (3), compounds of the formulae:

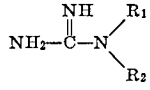


where R_1, R_2, R_3, R_4, R_5 and R_6 are as previously described are reacted with alkyl chlorides and alkyl bromides where alkyl has from 1 to 5 carbon atoms, alkanoyl bromides and alkanoyl chlorides where alkanoyl has from 2 to 7 carbon atoms, benzoyl chloride, benzoyl bromide, 2-methylbenzoyl halides, 3-methylbenzoyl halides and 4-methylbenzoyl halides where halide is bromide or chloride, 2-furoyl halide and 3-furoyl halide where halide is chloride or bromide, 2-thiophenoyl halide and 3-thiophenoyl halide where halide is chloride or bromide, allyl halide and methylallyl halide where halide is bromide or chloride. In the aforesaid reaction, at least a molar equivalent amount of the halide, and preferably an excess to ensure complete reaction, is added to a solution of the quinazoline in an organic solvent such as a methyl alkyl ketone, saturated aliphalic hydrocarbon or alkanol at room temperature. The reaction mixture is stirred for at least ½ hour and up to about 5 hours, depending, of course, on the size of the sample. While higher reaction times may be used they result in noxious fumes. Lower temperatures require longer periods of time for the compounds to react. The solid product is filtered from the reaction mixture and the product may be recrystallized from such solvents as methanol, ethanol, isopropanol, methylene chloride, chloroform, or the like.

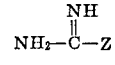
In method (4) 2-aminobenzonitriles of the formula:



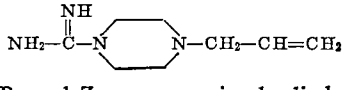
where R_5 and R_6 are as previously disclosed, are reacted with guanidines of the formulae:



and

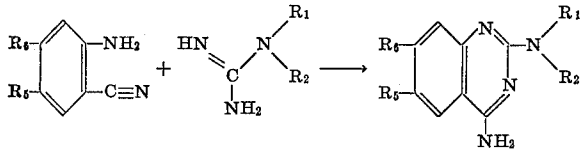


such as

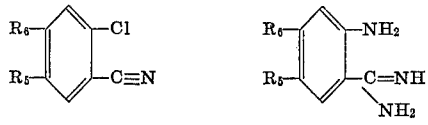


where R_1, R_2 and Z are as previously disclosed. In this method, the benzonitrile is dissolved in an inert high-boiling solvent such as dimethylformamide, dimethyl sulfoxide, ethylene glycol, or the like. A molar equivalent amount and preferably and excess of the guanidine is added and the mixture is heated at about 150° C. for from about 4 to 15 hours.

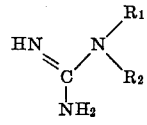
While lower temperatures may be employed for longer periods of time, about 12 hours are preferable for 0.1 molar quantities of reactants to ensure complete reaction. After heating, the solution is concentrated in vacuo to a small volume, water is added, and the mixture is chilled. The solids which precipitate are filtered from the mixture and recrystallized from solvents such as methanol-water, and dried. The reaction is illustrated as follows:



In methods (5) and (6), the compounds of this invention are prepared by reacting compounds of the formulae:

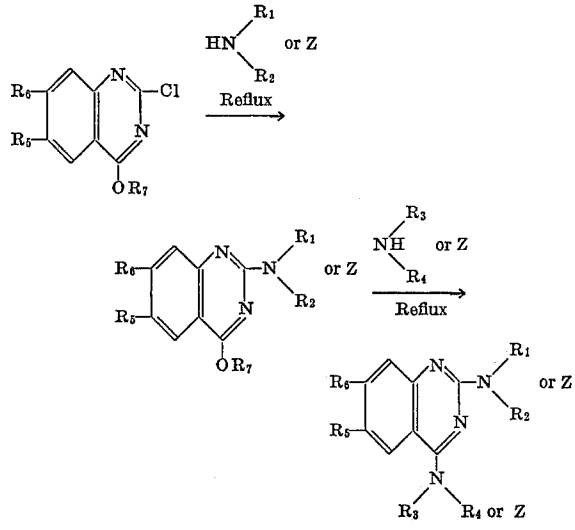


where R_5 and R_6 are as previously mentioned, with guanidines of the formula:



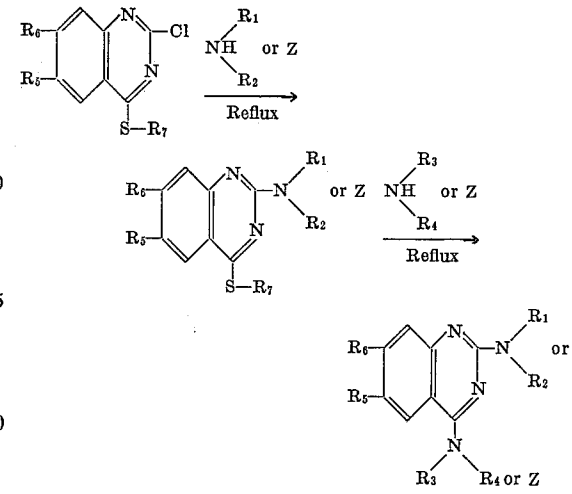
by the process described for method (4).

In method (7), 2-chloro-4-alkoxy - 6,7 - disubstituted-quinazolines whose preparation is described in Curd, Landquist and Rose, J. Chem. Soc., 1947, pages 775–783, are reacted at reflux with an amino compound in alcohol for several hours to obtain the 2-amino-4-alkoxy-6,7-di-substituted-quinazoline. The 4-position is then reacted with the same or a different amino compound at higher temperatures to obtain substitution on that position. The reaction sequence is as follows:



wherein R_1, R_2, R_3, R_4, R_5, R_6 and Z are as previously mentioned and wherein R_7 is methyl, ethyl, phenyl or benzyl.

In method (8), 2-chloro-4-alkylthio - 6,7 - disubstituted-quinazolines are reacted with amino compounds in refluxing alcohol to obtain 2-substituted amino-4-substituted amino - 6,7 - disubstituted-quinazolines. The reaction sequence is as follows:



wherein R_1, R_2, R_3, R_4, R_5, R_6, R_7 and Z are as previously disclosed.

The compounds of this invention are administered to hypertensive subjects either alone or in combinations with pharmaceutically-acceptable carriers. The proportion of active ingredient to carrier is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice. For example, they are administered in tablet form with such excipients as lactose, sodium citrate, calcium carbonate and dicalcium phosphate. Various disintegrants such as starch, alginic acid and certain complex silicates together with lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often used. For oral administration in capsule form, preferred materials are lactose and high molecular weight polyethylene glycols. When aqueous suspensions are desired, the essential active ingredients are combined with emulsifying and/or suspending agents. Diluents such as ethanol, propylene glycol, glycerine and various combinations of diluents are employed. For parenteral administration, solutions of the active ingredients in combination with other solutes such as glucose or saline are used. Such aqueous solutions should be suitably buffered if necessary to render them isotonic.

The dosage required to reduce blood pressure in hypertensive subjects will be determined by the nature and the extent of the hypertension. Generally, small dosages will be administered initially with a gradual increase in dosage until the optimum level is determined. It will generally be found that when the composition is administered orally, larger quantities of the active ingredient will be required to produce the same level of blood pressure reduction as produced by a smaller quantity administered parenterally. In general, from about 0.02 to 200 milligrams of active ingredient per kilogram of body weight administered in single or multiple dosage units effectively reduces blood pressure in hypertensive subjects. Tablets containing 0.5 to 50 milligrams of active ingredient are particularly useful.

The following examples are given by way of illustration and are not to be construed as limiting the invention in any way. Many variations of the invention are possible within the spirit of the invention.

EXAMPLE I

2-chloro-4-amino-6,7-dimethoxyquinazoline

To 800 ml. of a solution of anhydrous ammonia in tetrahydrofuran at room temperature is added 30 g. of 2,4-dichloro-6,7-dimethoxyquinazoline [F.H.S. Curd et. al., J. Chem. Soc., p. 1759 (1948)]. The mixture is stirred for 44 hours. The precipitate (29 g., M.P. 267–268° C.)

is filtered and recrystallized from methanol to yield 19 g. of 2-chloro-4-amino-6,7-dimethoxyquinazoline, M.P. 302° C. (dec.).

Analysis.—Calcd. for $C_{10}H_{10}N_3O_2Cl$ (percent): C, 50.11; H, 4.20; N, 17.53; Cl, 14.79. Found (percent): C, 49.99; H, 4.27; N, 17.52; Cl, 14.82.

EXAMPLE II

2,4-diamino-6,7-dimethoxyquinazoline

To a pressure bottle is added 7.78 g. of 2,4-dichloro-6,7-dimethoxyquinazoline in 100 ml. of ethanolic ammonia. The mixture is heated at 160° C. for 65 hours. The clear solution is evaporated to dryness and the residue is crystallized from dimethylformamide/water to yield 8.44 g. of product melting at 297–299° C. This product is dissolved in 400 ml. of hot water. The solution is made alkaline with sodium bicarbonate and the resulting precipitate is filtered, washed with water and dried to yield 6.6 g. of 2,4-diamino-6,7-dimethoxyquinazoline, M.P. 242–231° C. Recrystallization from water gives a product melting at 244–246° C.

EXAMPLE III

2,4-diamino-6,7-dimethoxyquinazoline dihydrochloride

The dihydrochloride of 2,4-diamino-6,7-dimethoxyquinazoline is prepared by dissolving the base in hot ethanol and adding an ethanolic hydrochloric acid solution to precipitate the salt.

In the same manner, acid addition salts are prepared, in lieu of hydrochloric, acid, sulfuric, nitric, hydriodic, hydrobromic, phosphoric and metaphosphoric acids, as well as salts of organic acids such as tartaric, acetic, citric, malic, benzoic, glycollic, gluconic, gulonic, succinic, arylsulfonic, e.g., p-toluenesulfonic acids and the like.

EXAMPLE IV

2,4-di-(N,N-diphenylamino)-6,7-dimethoxyquinalozine

To a pressure bottle is added 7.78 g. of 2,4-dichloro-6,7-dimethoxyquinazoline in 100 ml. of a 25% solution of diphenylamine in ethanol. The mixture is heated at 160° C. for 65 hours. The clear solution is evaporated to dryness and the residue is recrystallized from dimethylformamide/water to yield the product. The product is dissolved in 400 ml. of hot water. The solution is made alkaline with sodium bicarbonate and the resulting precipitate is filtered. washed with water and dried to yield 2,4-di(N,N-diphenylamino)-6,7-dimethoxyquinazoline.

EXAMPLE V

2-(N,N-dibenzylamino)-4-(N,N-diethylamino)-6,7-dimethoxyquinazoline

To 800 ml. of a solution of diethylamine in tetrahydrofuran at room temperature is added 30 g. of 2,4-dichloro-6,7-dimethoxyquinazoline. The mixture is stirred for 48 hours. The precipitate is filtered and recrystallized from methanol. To 5 grams of the product is added a 25% solution of dibenzylamine in ethanol. The mixture is heated at 160° C. for 16 hours in a pressure bottle. The solvent is evaporated and the product is recrystallized from methanol/water.

EXAMPLE VI

A number of 2,4-disubstituted-amino-6,7-dimethoxyquinazolines and their pharmaceutically-acceptable acid addition salts are prepared in the same manner as Examples III, IV and V with 2,4-dichloro-6,7-dimethoxyquinazoline and the appropriate amino compound. The products of these reactions are given in Table II.

EXAMPLE VII

2,4-dichloro-6-methoxy-7-amyloxyquinazoline

To 20 grams of 4-amyloxy-5-methoxy anthranilic acid in acetic acid (100 ml.) is added a suspension of sodium cyanate (11 g.) in water (50 gml.) and stirred well. After 1 hour, 2-ureido-4-amyloxy-5-methoxy benzamide is collected, washed and recrystallized from water. Twenty grams of the product is heated with 8 N hydrochloric acid (50 ml.) on a steam bath for 1 hour. The resulting product is stirred with 35% aqueous sodium hydroxide (50 ml.) to form the sodium salt. The salt is filtered, redissolved in 500 ml. hot water and re-precipitated with acetic acid to give 2,4-dihydroxy-6-methoxy-7-amyloxyquinazoline. The product is dried and converted to 2,4-dichloro-compound by refluxing 10 grams of the dihydroxy material with 16 g. phosphorous pentachloride and 10 ml. phosphoryl chloride for several hours. After removal of the phosphoryl chloride, the product is distilled from the flask under reduced pressure.

EXAMPLE VIII

2,4-dichloro-6-amyloxy-7-methoxyquinazoline

The compound is prepared from 4-methoxy-5-amyloxyanthranilic acid according to the procedure of Example VII.

EXAMPLE IX

2,4-dichloro-6,7-diamyloxyquinazoline

To 20 grams of 4,5-diamyloxyanthranilamide is acetic acid (100 cc.) is added a suspension of 11 g. sodium cyanate in 50 ml. water and stirred well. After 1 hour, 2-ureido-4,5-diamyloxybenzamide is collected, washed and recrystallized from water. Twenty grams of the product is heated with 8 N hydrochloric acid (45 cc.) on a steam bath for 1 hour. The resulting product is stirred with 35% sodium hydroxide (50 cc.) to form the sodium salt. The salt is filtered, redissolved in 500 cc. hot water and re-precipitated with acetic acid to give 2,4-dihydroxy-6,7-diamyloxyquinazoline. The product is dried and converted to 2,4-dichloro-6,7-diamyloxyquinazoline by refluxing 10 grams of dihydroxy compound with 16 g. phosphorous pentachloride and 10 cc. phosphoryl chloride for six hours. After removal of the phosphoryl chloride, the product is distilled from the flask under reduced pressure.

EXAMPLE X

2,4-dichloro-6,7-diethoxyquinazoline

The 2,4-dichloro-6,7-diethoxyquinazoline is prepared by the procedure of Example IX starting with 4,5-diethoxyanthranilamide, 4,5-diethoxyanthranilic acid or a lower alkyl ester such as methyl 4,5-diethoxyanthranilate.

EXAMPLE XI

A series of 2,4-disubstituted amino-6,7-diamyloxyquinazolines and their pharmaceutically-acceptable acid addition salts are prepared from 2,4-dichloro-6,7-diamyloxyquinazoline by the procedures of Examples III, IV, V and IX. These compounds are listed in Table II.

EXAMPLE XII

A series of 2,4-disubstituted amino-6,7-diethoxyquinazolines and their pharmaceutically-acceptable acid addition salts are prepared from 2,4-dichloro-6,7-diethoxyquinazoline according to the procedure of Examples II, III and VI. These compounds are listed in Table II.

EXAMPLE XIII

2,4-dichloro-6-methoxyquinazoline

The 2,4-dichloro-6-methoxyquinazoline is prepared by the procedure of Example VIII with 5-methoxyanthranilic acid, 5-methoxyanthranilamide or a lower alkyl ester of 5-methoxyanthranilic acid such as methyl 5-methoxyanthranilate.

EXAMPLE XIV

2,4-dichloro-7-methoxyquinazoline

The 2,4-dichloro - 7 - methoxyquinazoline is prepared from 4 - methoxyanthranilamide, 4 - methoxyanthranilic

acid or a lower alkyl ester of the acid according to the procedure of Example VIII.

EXAMPLE XV

2,4-disubstituted-6-methoxyquinazolines and 2,4-disubstituted-7-methoxyquinazolines

The substituted 6- and 7-methoxyquinazolines and their pharmaceutically-acceptable acid addition salts are prepared according to the procedures of Examples II, III, XII and XIII. These compounds are listed in Table II.

EXAMPLE XVI

2,4-dichloro-6-(7)-amyloxyquinazoline

The 2,4-dichloro-6-amyloxyquinazoline and the 2,4-dichloro-7-amyloxyquinazoline and their pharmaceutically-acceptable acid addition salts are prepared according to the procedure of Example VIII from 5-amyloxyanthranilamide and 4-amyloxyanthranilamide, respectively, or the corresponding acids and lower alkyl esters.

EXAMPLE XVII

2,4-disubstituted-6-(7)-amyloxyquinazoline

The 2,4-disubstituted-6-(7)-amyloxyquinazolines and their corresponding pharmaceutically-acceptable acid addition salts are prepared from the corresponding dichloro-compound according to the procedures of Examples II, III and XV. These compounds are listed in Table II.

EXAMPLE XVIII

2,4-dichloro-6-methoxy-7-amyloxyquinazoline

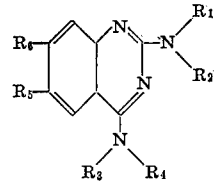
The 2,4-dichloro-6-methoxy-7-amyloxyquinazoline is prepared by the procedure of Example VIII with 4-amyloxy-5-methoxyanthranilamide, 4-amyloxy-5-methoxyanthranilic acid or its lower alkyl esters.

EXAMPLE XIX

2,4-disubstituted-6-methoxy-7-amyloxyquinazoline

The 2,4-disubstituted-6-methoxy-7-amyloxyquinazoline and its pharmaceutically-acceptable acid addition salts are prepared by the procedures of Examples II, III and XVII. These compounds are listed in Table II.

TABLE II



R_1	R_2	R_3	R_4	R_5	R_6
$CH_2=CH-CH_2-$	$CH_2=CH-CH_2-$	$CH_2=CH-CH_2-$	$CH_2=CH-CH_2-$	CH_3O-	CH_3O-
$CH_2=CH-(CH_2)_3-$	$CH_2=CH-(CH_2)_3-$	$CH_2=CH-(CH_2)_3-$	$CH_2=CH-(CH_2)_3-$	CH_3O-	CH_3O-
$C_6H_5-CH_2-$	C_6H_5-	$C_6H_5-CH_2-$	C_6H_5-	CH_3O-	CH_3O-
2-OH—C_6H_4-	C_6H_5-	$C_6H_5-CH_2-$	C_6H_5-	CH_3O-	H—
4-Cl—C_6H_4-	2-HO—CH_2-	$C_6H_5-CH_2-$	2-HO—CH_2-	CH_3O-	CH_3O-
2-CH_3O—C_6H_4-	C_6H_5-	2-CH_3O—C_6H_4-	C_6H_5-	H—	CH_3O-
C_6H_5-	C_6H_5-	C_6H_5-	C_6H_5-	CH_3O-	H—
C_6H_5-	H—	C_6H_5-	H—	H—	CH_3O-
$C_6H_5-CH_2-$	$C_6H_5-CH_2-$	H—	H—	C_2H_5O-	C_2H_5O-
4-Cl—C_6H_4-	H-	4-Cl—C_6H_4-	H-	C_2H_5O-	H—
3,4-Cl_2—C_6H_3-	H—	H—	H—	C_3H_7O-	C_3H_7O-
3-Br—C_6H_4-	3-Br—C_6H_4-	H—	H—	C_3H_7O-	C_3H_7O-
2-CH—C_6H_4	H—	2-OH—C_6H_4-	H—	C_4H_9O-	H—
HO—$(CH_2)_5-$	HO—$(CH_2)_5-$	HO—$(CH_2)_5-$	H—	H—	$C_5H_{11}O-$
2-CH_3O—C_6H_4-	H—	2-CH_3O—C_6H_4-	H—	$C_5H_{11}O-$	$C_5H_{11}O-$
3-CH_3O—C_6H_4-	3-CH_3O—C_6H_4-	H—	H—	H—	$C_5H_{11}O-$
2-$C(F)_3CH_2-$	H—	H—	H—	CH_3O-	CH_3O-
2-$C(F)_3$—CH_2-	H—	H—	H—	C_2H_5O-	CH_3O-
4-($C_6H_{13}O-$)C_6H_4-	4-($C_6H_{13}O-$)C_6H_4-	H—	H—	$C_5H_{11}O-$	$C_5H_{11}O-$
2,4-$(CH_3)_2$—C_6H_3-	H—	2,4-$(CH_3)_2$—C_6H_5-	H—	CH_3O-	$C_5H_{11}O-$
2,4-(C_6H_{13})—C_6H_5-	2,4-($C_6H_{13}-$)C_6H_3-	H—	H—	CH_3O-	C_2H_5O-
2-(C_6H_{13})C_6H_4	H—	2-($C_6H_{13}-$)C_6H_4-	H—	$C_5H_{11}O-$	CH_3O-
2,4-$Br_2C_6H_3-$	2,4-$Br_2C_6H_3$	H—	H—	C_2H_5O- L	CH_3O-
2-CH_3—C_6H_4-	H—	2-CH_3—C_6H_4-	H—	H—	C_2H_5O-
3-CH_3—C_6H_4-	3-CH_3—C_6H_4-	2-CH_3—C_6H_4-	H—	H—	CH_3O-
C_6H_5-	H—	$C_6H_5-CH_2-$	$C_6H_5-CH_2-$	CH_3O-	C_2H_5O-
5-Cl—C_6H_5-	3-Cl—C_6H_5-	HO—CH_2-CH_2	H—	H—	C_3H_7O-
2-HO—C_6H_4-	H—	2-HO—C_6H_4-	H—	H—	$C_5H_{11}C-$
2-F—C_6H_4-	H—	2,4-F_2—C_6H_3-	H—	CH_3O-	CH_3O-
3-F—C_6H_4-	3-F—C_6H_4-	3-F—C_6H_4-	3-F—C_6H_4-	CH_3O-	CH_3O-
H—	H—	H—	H—	CH_3O-	CH_3O-
$C_6H_5-C_2H_4-$	$C_6H_3-C_2H_4-$	$C_6H_5-C_2H_4-$	$C_6H_5-C_2H_4-$	CH_3O-	H—

EXAMPLE XX

2-amino-4-morpholino-6,7-dimethoxyquinazoline

To 80 ml. of a 25% solution of morpholine in tetrahydrofuran at room temperature is added 30 g. 2,4-dichloro-6,7-dimethoxyquinazoline. The mixture is stirred for 48 hours. The precipitate is filtered and recrystallized from methanol. To 5 g. of the product is added 100 ml. of ethanolic ammonia. The mixture is heated at 160° C. for 16 hours in a pressure bottle. The solvent is evaporated and the residue is recrystallized from methanol/water.

EXAMPLE XXI

The 2-amino-4-substituted-6,7-dimethoxyquinazolines and their pharmaceutically-acceptable acid addition salts are prepared from 2,4-dichloro-6,7-dimethoxyquinazoline according to the procedures of Examples XX and III. These compounds are listed in Table III.

EXAMPLE XXII

2-dimethylamino-4-morpholino-6,7-dimethoxyquinazoline

To 80 ml. of a 25% solution of morpholine in tetrahydrofuran at room temperature is added 30 g. 2,4-dichloro-6,7-dimethoxyquinazoline prepared by the procedure in Example I. The mixture is stirred for 48 hours. The precipitate is filtered and recrystallized from methanol. To 5 5. of the product is added 12 grams of a 25% solution of dimethylamine in ethanol. The mixture is heated at 160° C. for 16 hours in a pressure bottle. The solvent is evap-

orated and the residue is recrystallized from methanol/water.

EXAMPLE XXIII

The 2,4-disubstituted - 6,7 - dimethoxyquinazolines and their pharmaceutically-acceptable acid addition salts are prepared according to the procedures of Examples III and XXII. These compounds are listed in Table III.

EXAMPLE XXIV

2-amino-4-morpholino-6-methoxy-7-amyloxyquinazoline

This compound is prepared from 2,4-dichloro-6-methoxy-7-amyloxyquinanzoline according to the procedures of Examples VII and XX. The dihydrochloride salt is prepared from the base compound according to the procedure of Example III.

EXAMPLE XXV

The 2-amino-4-substituted-6-methoxy - 7-amyloxyquinazolines are prepared according to the procedure of Example XXIV substituting the appropriate amino compound for morpholine in the procedure. These compounds are illustrated in Table III.

EXAMPLE XXVI

The 2-amino-4-substituted - 6(7)methoxyquinazolines and the 2,4-disubstituted 6(7)methoxyquinazolines are prepared according to the procedures of Examples XIII, XIV, XXIII and XXI. The dihydrochloride salt is prepared according to the procedure of Example III. These compounds are listed in Table III.

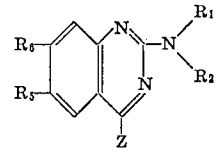
EXAMPLE XXVII

The 2,4-disubstituted - 6(7)amyloxyquinazolines and the 2-amino-4-substituted 6(7)amyloxyquinazolines are prepared according to the procedures of Examples XVI, XV and XIX. The dihydrochloride salt is prepared according to the procedure of Example III. These compounds are listed in Table III.

EXAMPLE XXVIII

The 2,4-disubstituted-6(7)-ethoxyquinazolines and the 2-amino - 4-substituted-6(7)-ethoxyquinazolines are prepared from 4-ethoxyanthranilic acid, 5-ethoxyanthranilic acid, the amides and lower alkyl esters according to the procedures of Examples XV, XVI, XIX and XXI. The dihydrochloride salts are prepared according to the procedure of Example IIII. These compounds are listed in Table III.

TABLE III



R_1	R_2	Z	R_5	R_6
H—	H—	piperidino-	CH_3O—	CH_3O—
H—	H—	4-methyl-1-piperazinyl-	CH_3O—	H—
H—	H—	4-pentyl-1-piperazinyl	H—	CH_3O—
CH_2=CH—CH_2—	CH_2=CH—CH_2—	4-hydroxyethyl-1-piperazinyl-	C_2H_5O—	C_2H_5O—
CH_2=CH—$(CH_2)3$—	CH_2=CH—$(CH_2)3$—	morpholino-	H—	C_2H_5O—
C_6H_5—	C_6H_5—	2,6-dimethylmorpholino-	C_2H_5O—	H—
C_6H_5—	H—	2,6-dipentylmorpholino-	C_3H_7O—	C_3H_7O—
C_6H_5—C_2H_4—	C_6H_4—C_2H_4	3-oxo-1-piperazinyl-	C_3H_7O—	H—
2-Cl—C_6H_4—	2-Cl—C_6H_4—	4-acetyl-1-piperazinyl	H—	C_3H_7O—
3-Cl—C_6H_4—	H—	4-phenyl-1-piperazinyl-	C_4H_9O—	C_4H_9O—
4-Cl—C_6H_4—	4-Cl—C_6H_4—	pyrrolidyl-	H—	C_4H_9O—
C_6H_5—	C_6H_5—	cyclopropylamino	H—	C_3H_7O—
2-Cl—C_6H_4—	H—	cyclobutylamino	C_2H_5O—	C_2H_5O—
CH_2=CH—CH_2	H—	cycloheptylamino	C_3H_7O—	C_3H_7O—
2-Br—C_6H_4	2-Br—C_6H_4	4-valeryl-1-piperazinyl-	C_4H_9O—	H—
3-Br—C_6H_4—	H—	4-valeryl-1-piperazinyl-	$C_5H_{11}O$—	$C_5H_{11}O$—
2-F—C_6H_4—	2-F—C_6H_4—	pyrrolidyl-	H—	$C_5H_{11}O$—
2,4-$Cl_2C_6H_3$—	2,4-Cl_2—C_6H_3—	piperidino-	$C_5H_{11}O$—	H—
4-Br—C_6H_4—	4-Br—C_6H_4—	piperidino-	CH_3O—	CH_3O—
2-HO—C_6H_4	2-HO—C_6H_4—	4-methyl-piperazinyl-1-	CH_3O—	CH_3O—
3-HO—C_6H_4—	H—	4-pentyl-piperazinyl-1-	CH_3O—	H—
4-HO—C_6H_4—	H—	4-hydroxymethyl-piperazinyl-1-	H—	CH_3O—
HO—CH_2—CH_2—	H—	morpholino-	C_2H_5O—	C_2H_5O—
HO—CH_2—$(CH_2)_4$—	HO—CH_2—$(CH_2)_4$—	2,6-dimethylmorpholino	H—	C_2H_5O—
2-CH_3—C_6H_4—	2-CH_3—C_6H_4—	2,6-dipentylmorpholino	C_3H_7O—	C_3H_7O—
3-CH_3—C_6H_4—	H—	4-benzoyl-1-piperazinyl	$C_5H_{11}O$—	H—
4-CH_3—C_6H_4—	H—	morpholino-	CH_3O—	$C_5H_{11}O$—
2,6-$(CH_3)_2C_6H_3$—	H—	1-azacycloheptyl-	$C_5H_{11}O$—	CH_3O—
2-CH_3O—C_6H_4—	2-CH_3O—C_6H_4—	1-azacyclooctyl-	C_2H_5O—	CH_3O—
3-CH_3O—C_6H_4—	3-CH_3O—C_6H_4—	1-piperazinyl-	C_3H_7O—	$C_5H_{11}O$—
4-CH_3O—C_6H_4—	H—	1-piperazinyl-	CH_3O—	H—
2-$C_6H_{13}O$—C_6H_4—	H—	3-oxo-1-piperazinyl-	H—	CH_3O—
3-$C_6H_{13}O$—C_6H_4—	H—	4-acetyl-1-piperazinyl-	H—	$C_5H_{11}O$—
C_6H_5—CH_2—	C_6H_5—CH_2—	piperidino-	CH_3O—	CH_3O—
CH_2=CH—CH_2—	C_6H_5—	piperidino-	C_2H_5O—	H—
2-Cl—C_6H_4—	C_6H_5—	pyrrolidyl-	H—	CH_3O—
4-HO—C_6H_4—	3-CH_3O—C_6H_4—	morpholino-	H—	CH_3O—
HO—CH_2—CH_2—	C_6H_5—CH_2—	morpholino-	C_2H_5O—	C_2H_5O—
2-C_6H_{13}—C_6H_5—	H—	1-piperazinyl-	H—	CH_3O—
3-F—C_6H_4—	H—	morpholino	CH_3O—	$C_5H_{11}O$—
4-F—C_6H_4—	H—	2,6-dimethylmorpholino-	CH_3O—	C_2H_5O—
4-F—C_6H_4	4-F—C_6H_4—	pyrrolidyl-	CH_3O—	H—
3-C_6H_{13}—C_6H_4	H—	pyrrolidyl-	$C_5H_{11}O$—	C_2H_5O—
4-C_6H_{13}—C_6H_4—	4-C_6H_{13}—C_6H_4—	pyrrolidyl-	H—	C_2H_5O—

EXAMPLE XXIX

2-(4-methyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazolines

To 5 grams of 2-chloro-4-amino - 6,7-dimethoxyquinazoline prepared as in Example I, is added 20 grams of a 25% solution of 4-methylpiperazine in ethanol. The mixture is heated at 160° C. for 16 hours in a pressure bottle. The solvent is then evaporated and the residue is recrystallized from methanol/water.

EXAMPLE XXX

2-morpholino-4-(N,N-dibenzylamino)-6,7-diamyloxyquinazoline

To 30 grams 2,4-dichloro - 6,7-diamyloxyquinazoline prepared as in Example IX is added 100 ml. of a 10% solution of dibenzylamine in tetrahydrofuran at room temperature. The mixture is stirred for 48 hours. The resulting precipitate is filtered and recrystallized from methanol. To 5 grams of the product is added 50 ml. of a 25% solution of morpholine in ethanol. The mixture is heated at 160° C. for 16 hours in a sealed pressure bottle. The solvent is evaporated and the product is recrystallized from methanol/water.

EXAMPLE XXXI

The 2-substituted - 4-amino-6,7-dimethoxyquinazolines are prepared as in Example XXIX. The dihydrochloride salt is prepared according to the procedure of Example III. These compounds are listed in Table IV.

EXAMPLE XXXII

The 2,4 - disubstituted - 6,7 - dimethoxyquinazolines where carbon 2 is substituted with a heterocyclic nitrogen compound, are prepared as in Example XXX. These compounds are listed in Table IV.

EXAMPLE XXXIII

The 2,4-disubstituted - 6,7-diamyloxyquinazolines are prepared as in Example XXX from 2,4-dichloro-6,7-diamyloxyquinazoline. The dihydrochloride salts are prepared as in Example III. These compounds are listed in Table IV.

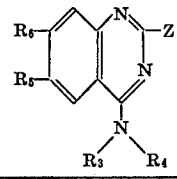
EXAMPLE XXXIV

The 2,4-disubstituted 6-methoxy - 7-amyloxyquinanzolines are prepared from 2,4-dichloro-6-methoxy-7-amyloxyquinazoline according to the procedure of Example XXX. The pharmaceutically-acceptable acid addition salts are prepared according to the procedure of Example III. These compounds are listed in Table IV.

EXAMPLE XXXV

The 2,4-disubstituted - 6(7)methoxyquinazolines are prepared from 2,4-dichloro - 6-methoxyquinazoline and 2,4-dichloro-7-methoxyquinazolines according to the procedure of Example XXX. The pharmaceutically-acceptable acid addition salts are prepared according to the procedure of Example III. The compounds are listed in Table IV.

TABLE IV



R_3	R_4	Z	R_5	R_6
H—	C_6H_5	4-alkyl-1-piperazinyl-	CH_3O—	CH_3O—
H—	H—	2,6-dipentylmorpholine-	$C_5H_{11}O$—	$C_5H_{11}O$—
CH_2=CH—CH_2—	CH_2=CH—CH_2—	2,6-dimethylmorpholino-	$C_5H_{11}O$—	CH_3O—
CH_2=CH—$(CH_2)_3$—	H—	pyrrolidyl-	$C_5H_{11}O$—	C_2H_5O—
C_6H_5—	C_6H_5—	morpholino-	$C_5H_{11}O$—	C_3H_7O—
C_6H_5—	H—	4-hydroxyethyl-1-piperazinyl-	C_4H_9O—	C_4H_9O—
HO—CH_2—CH_2—	HO—CH_2—CH_2	piperidino-	$C_5H_{11}O$—	C_4H_9O—
HO—CH_2—CH_2—	H—	4-hydroxypentyl-1-piperazinyl	CH_3O—	H—
HO—$(CH_2)_5$—	HO—$(CH_2)_5$—	morpholino-	CH_3O—	C_2H_5O—
HO—$(CH_2)_5$—	H—	1-azacycloheptyl-	CH_3O—	C_3H_7O—
2-CH_3O—C_6H_4—	2-CH_3O—C_6H_4—	1-azacyclooctyl-	H—	C_3H_7O—
2-CH_3O—C_6H_4—	H—	4-phenyl-1-piperazinyl-	H—	$C_5H_{11}O$—
3-CH_3O—C_6H_4—	H—	4-methyl-1-piperazinyl-	C_2H_5O—	H—
4-CH_3O—C_6H_4—	4-CH_3O—C_6H_4	4-pentyl-1-piperazinyl-	C_2H_5O—	H—
4-CH_3O—C_6H_4—	H—	3-oxo-1-piperazinyl	CH_3O—	CH_3O—
C_6H_5—CH_2—	C_6H_5—	morpholino-	CH_3O—	C_2H_5O—
4-CH_3O—C_6H_4—	C_6H_5—	morpholino-	CH_3O—	$C_5H_{11}O$—
3-Br—C_6H_4—	C_6H_5—	pyrrolidyl-	CH_3O—	CH_3O—
2-CH_3O—C_6H_4—	HO—$(CH_2)_5$—	piperidino-	H—	CH_3O—
HO—CH_2—CH_2	C_6H_5—CH_2—	pyrrolidyl-	H—	CH_3O—
HO—CH_2—CH_2—	C_6H_5—CH_2—	cyclopropylamino	H—	C_3H_7O—
HO—CH_2—CH_2—	HO—CH_2—CH_2—	cycloheptylamino	CH_3O—	CH_3O—
C_6H_5—	C_6H_5—	cyclohexylamino	CH_3O—	CH_3O—
2-C_6H_{13}—C_6H_4—	2-C_6H_{13}—C_6H_4—	morpholino	CH_3O—	CH_3O—
3-C_6H_{13}—C_6H_4—	H—	piperidino-	H—	CH_3O—
4-C_6H_{13}—C_6H_4—	4-C_6H_{13}—C_6H_4—	4-methyl-1-piperazinyl-	CH_3O—	H—
2-Cl—C_6H_4—	2-Cl—C_6H_4	4-pentyl-1-piperazinyl-	C_2H_5O—	C_2H_5O—
2-Cl—C_6H_4—	H—	4-phenyl-1-piperazinyl	H—	C_2H_5O
3-Cl—C_6H_4—	H—	3-oxo-1-piperazinyl-	C_2H_5O—	H—
4-Cl—C_6H_4	4-Cl—C_6H_4	4-acetyl-1-piperazinyl-	$C_5H_{11}O$—	$C_5H_{11}O$—
2-Br—C_6H_4—	H—	4-n-valeryl-1-piperazinyl-	H—	$C_5H_{11}O$—
3-Br—C_6H_4—	H—	4-benzoyl-1-piperazinyl-	$C_5H_{11}O$—	H—
4-Br—C_6H_4—	4-Br—C_6H_4—	2,6-dimethylmorpholino-	CH_3O—	$C_5H_{11}O$—
2-F—C_6H_4—	2-F—C_6H_4—	2,6-dipentylmorpholino	$C_5H_{11}O$—	CH_3O—
3-F—C_6H_4—	H—	1-azacycloheptyl-	C_2H_5O—	CH_3O—
4-F—C_6H_4—	4-F—C_6H_4—	1-azacyclooctyl-	C_2H_5O—	$C_5H_{11}O$—
2-$C(F_3)$—CH_2—	H—	pyrrolidyl-	CH_3O—	CH_3O—
2-$C_6H_{13}O$—C_5H_4—	H—	pyperidino-	CH_3O—	H—
3-$C_6H_{13}O$—C_5H_4—	H—	4-methyl-1-piperazinyl-	CH_3O—	CH_3O—
4-$C_6H_{13}O$—C_5H_4—	4-$C_6H_{13}O$—C_6H_4—	4-pyrrolidyl-	C_2H_5O—	H—
C_6H_5—CH_2—	C_6H_5—CH_2—	4-pentyl-1-piperazinyl-	C_2H_5O—	C_2H_5O—
C_6H_5—CH_2—	H—	morpholino-	H—	CH_3O—
C_6H_5—CH_2—CH_2—	C_6H_5—CH_2—CH_2	4-n-valeryl-1-piperazinyl-	H—	C_2H_5O—
C_6H_5—CH_2—	H—	4-acetyl-1-piperazinyl-	H—	$C_5H_{11}O$—
2-CH_3—C_6H_4—	2-CH_3—C_6H_4—	3-oxo-1-piperazinyl-	$C_5H_{11}O$—	$C_5H_{11}O$—
2-CH_3—C_6H_4—	H—	4-benzoyl-1-piperazinyl-	$C_5H_{11}O$—	H—
3-CH_3—C_6H_4—	H—	4-phenyl-1-piperazinyl-	$C_5H_{11}O$—	CH_3O—
4-CH_3—C_6H_4—	4-CH_3—C_6H_4—	1-azacycloheptyl-	CH_3O—	$C_5H_{11}O$—
2,6-$(CH_3)_2$—C_6H_3—	H—	1-azacycloocytl-	CH_3O—	C_2H_5O—

EXAMPLE XXXVI

2-(N,N-dimethylamino)-4-amino-6,7-dimethoxyquinazoline

To 5 grams of 2-chloro-4-amino-6,7-dimethoxyquinazoline, prepared according to the procedure of Example I, is added 50 ml. of a 25% solution of dimethylamine in ethanol. The mixture is heated for 16 hours at 160° C. in a sealed pressure bottle. The solvent is evaporated

and the residue is crystallized from methanol/water to yield the product. M.P. 219–222° C.

EXAMPLE XXXVII

2-(N,N-dimethylamino)-4-amino-6,7-dimethoxyquinazoline

To 5 grams of 2-chloro-4-amino-6,7-dimethoxyquinazoline is added 50 ml. of a 25% solution of diethylamine in ethanol. The mixture is heated for 16 hours at 160° C. in a pressure bottle. The solvent is evaporated and the residue (6.9 g.) is crystallized from methanol/water to yield 3.3 grams of product melting at 179–180° C.

Analysis.—Calcd. for $C_{14}H_{20}N_4O_3$ (percent): C, 60.85; H, 7.30; N, 20.28. Found (percent): C, 61.07; H, 7.17; N, 20.31.

EXAMPLE XXXVIII

2-(N,N-diethylamino)-4-amino-6,7-dimethoxquinazoline dihydrochloride

The dihydrochloride is prepared by dissolving the base in hot ethanol and adding ethanolic hydrochloric acid solution to precipitate the salt. M.P. 259–260° C.

EXAMPLE XXXIX

2-(N,N-diallylamino)-4-amino-6,7-dimethoxyquinazoline

The compound is prepared by the procedure of Example XXXVII using diallylamine in ethanol rather than diethylamine. The product melts 177–179° C. The dihydrochloride salt, prepared as in Example XXVIII, melts 227–229° C.

EXAMPLE XL

2-amino-4-(N,N-dimethylamino)-6,7-dimethoxyquinazoline

To 80 grams of a 10% solution of dimethylamine in tetrahydrofuran at room temperature is added 30 grams 2,4-dichloro-6,7-dimethoxyquinazoline. The mixture is stirred 48 hours. The resulting precipitate is filtered and recrystallized from methanol. To 5 grams of the product is added 100 ml. of ethanolic ammonia. This mixture is heated at 160° C. for 16 hours in a sealed pressure bottle. The solvent is evaporated and the residue is recrystallized from methanol/water.

EXAMPLE XLI

2-amino-4-(N,N-diamylamino)-6,7-diamyloxyquinazoline

To 30 grams of 2,4-dichloro-6,7-diamyloxyquinazoline prepared as in Example IX, is added 80 grams of a 10% solution of diamylamine in tetrahydrofuran. The mixture is stirred for 48 hours. The precipitate which forms is filtered and recrystallized from methanol. To 5 grams of the product is added 100 ml. ethanolic ammonia. This mixture is heated at 160° C. for 16 hours in a sealed pressure bottle. The solvent is evaporated and the residue is recrystallized from methanol/water.

EXAMPLE XLII

2-4-di(N,N-dimethylamino)-6,7-dimethoxyquinazoline

To 80 grams of a 10% solution of dimethylamine in tetrahydrofuran at room temperature is added 30 grams 2,4-dichloro-6,7-dimethoxyquinazoline. The mixture is stirred 48 hours. The resulting precipitate is filtered and recrystallized from methanol. To 5 grams of the product is added 20 grams of a 10% solution of dimethylamine in ethanol. The mixture is heated in a sealed pressure bottle at 160° C. for 16 hours. The solvent is evaporated and the residue is recrystallized from methanol/water. The product melts at 121–122° C. The hydrochloride melts at 243° C.

Analysis.—Calcd. for $C_{14}H_{20}O_2N_2HCl$ (percent): C, 53.76; H, 6.76; N, 17.91; Cl, 11.33. Found (percent): C, 53.42; H, 6.71; N, 17.84; Cl 11.16.

EXAMPLE XLIII

2,4-di(N,N-diamylamino)-6,(7)-dimethoxyquinazoline

This compound is prepared with diamylamine according to the procedure of Example XLII.

EXAMPLE XLIV

2,4-di(N,N-dimethylamino)-6,(7)-methoxyquinazoline

These compounds are prepared from 2,4-dichloro-6-methoxyquinazoline (Example XIII) and 2,4-dichloro-7-methoxyquinazoline (Example XIV) according to the procedure of Example XLII.

EXAMPLE XLV

2-methylamino-4-amino-6,7-dimethoxyquinazoline

This compound is prepared by the procedure of Example XXXVII by reacting 2-chloro-4-amino-6,7-dimethoxyquinazoline with an ethanolic solution of methylamine.

EXAMPLE XLVI

2-amylamino-4-amino-6,7-dimethoxyquinazoline

This compound is prepared by the procedure of Example XXXVII by reacting 2-chloro-4-amino-6,7-dimethoxyquinazoline with an ethanolic solution of amylamine.

EXAMPLE XLVII

2-N-ethylanilino-4-amino-6,7-dimethoxyquinazoline

This compound is prepared by the procedure of Example XXXVII by reacting 2-chloro-4-amino-6,7-dimethoxyquinazoline with N-ethylaniline.

EXAMPLE XLVIII

2-N-methylbutylamino-4-amino-6,7-dimethoxyquinazoline

This compound is prepared by the procedure of Example XXXVII by reacting 2-chloro-4-amino-6,7-dimethoxyquinazoline with N-methylbutylamine.

EXAMPLE XLIX

2-amino-4-N-methylbutylamino-6,7-dimethoxyquinazoline

This compound is prepared by the procedure of Example XL by reacting N-methylbutylamine with 2,4-dichloro-6,7-dimethoxyquinazoline.

EXAMPLE L

The biological activity of the compounds of this invention, particularly in regard to their effectiveness in reducing blood pressure in hypertensive subjects, is illustrated by the following tests on renal hypertensive dogs. The compounds were administered orally in capsule form. The effective dose level was that which lowered the blood pressure from 180/100 to 160/100 mm. Hg. The activity of the compounds is shown in Table XVIII.

Table XVIII

Hypotensive activity

Compound:	Minimum effective concentration, mg./kg.
2,4-diamino-6,7-dimethoxyquinazoline	2.50
2 - methylamino - 4 - amino-6,7-dimethoxyquinazoline	2.50
2 - ethylamino - 4 - amino-6,7-dimethoxyquinazoline	2.50
2 - n - propylamino - 4 - amino-6,7-dimethoxyquinazoline	2.50
2 - n - butylamino - 4 - amino - 6,7 - dimethoxyquinazoline	2.50
2 - isopropylamino - 4 - amino-6,7-dimethoxyquinazoline	1.25
2 - dimethylamino - 4 - amino - 6,7 - dimethoxyquinazoline	0.63
2 - diethylamino - 4 - amino-6,7-dimethoxyquinazoline	1.25
2 - N - methyl-(β-hydroxyethyl)amino-4-amino-6,7-dimethoxyquinazoline	10
2 - diallylamino - 4 - amino-6,7-dimethoxyquinazoline	10
2 - (4 - methyl - 1 - piperazinyl)-4-amino-6,7-dimethoxyquinazoline	2.50
2 - β,β,β - trifluoroethylamino - 4 - amino-6,7-dimethoxyquinazoline	2.50
2 - (4 - n - propyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline	2.5
2 - (diethanolamino) - 4-amino-6,7-dimethoxyquinazoline	10
2 - (dimethylamino) - 4 - methylamino-6,7-dimethoxyquinazoline	2.50
2,4 - di(diethylamino) - 6,7 - dimethoxyquinazoline	10
2,4 - di(N,N - dimethylamino)-6,7-dimethoxyquinazoline	10

EXAMPLE LI

Tablets

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 sufficient 2-dimethylamino-4-amino-6,7-dimethoxyquinazoline to provide tablets containing 20, 100 and 250 mg. of active ingredient.

EXAMPLE LII

Capsules

A blend is prepared containing the following ingredients:

Calcium carbonate, U.S.P.	17.6
Dicalcium phosphate	18.8
Magnesium trisilicate, U.S.P.	5.2
Lactone, U.S.P.	5.2
Potato starch	5.2
Magnesium stearate A	0.8
Magnesium stearate B	0.35

To this blend is added sufficient 2-(4-propyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline to provide capsules containing 20, 100 and 250 mg. of active ingredient.

EXAMPLE LIII

Injectable preparation

One thousand grams of 2-methylamino-4-amino-6,7-dimethoxyquinazoline are intimately mixed and ground with 2500 grams of sodium ascorbate. The ground dry mixture is filled into vials, sterilized with ethylene oxide and the vials sterilely stoppered. For intravenous administration sufficient water is added to the vials to form a solution containing 10 mg. of active ingredient per milliliter.

EXAMPLE LIV

Suspension

A suspension of 2-(N,N-diallylamino)-4-amino-6,7-dimethoxyquinazoline is prepared with the following composition:

Effective ingredient—31.42 g.
70% aqueous sorbitol—714.29 g.
Glycerine, U.S.P.—185.35 g.
Gum acacia (10% solution)—100.00 ml.
Polyvinyl pyrrolidone—0.5 g.
Water, distilled to make 1 liter.

To this suspension, various sweetening and flavoring agents may be added by choice. The suspension contains approximately 25 mg. of hypotensive agent per milliliter.

EXAMPLE LV

Solution

A solution of 2 - dimethylamino - 4 - methylamino-6,7-dimethoxyquinazoline is prepared with the following composition.

Effective ingredient—30.22 g.
Magnesium chloride hexahydrate—12.36 g.
Monoethanolamine—8.85 ml.
Propylene glycol—376 g.
Water—94 ml.

The solution has a concentration of 50 mg./ml. and is suitable for parenteral and especially for intramuscular administration.

EXAMPLE LVI

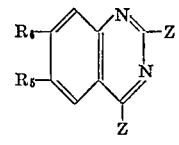
The methods employed for the preparation of the compounds of the previous examples are also used to prepare compounds having substituents other than alkoxy on positions 5, 6, 7 and 8 of the quinazoline nucleus. These compounds are prepared from substituted aromatic compounds such as those in Table XIX, followed by chlorination as described in Examples VII, VIII, IX and X. These compounds are as follows:

Table XIX

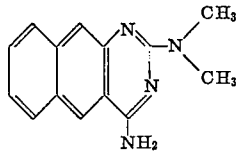
Substituted 2,4-dichloroquinazolines

Starting compound:	Substituents
Methyl 5-chloroanthranilate	6-chloro-
4-chloroanthranilic acid	7-chloro-
Methyl 3-bromoanthranilate	8-bromo-
Methyl 6-fluoroanthranilate	5-fluoro-
Methyl 4-fluoroanthranilate	7-fluoro-
4,5-dimethylanthranilamide	6,7-dimethyl-
5-pentylanthranilic acid	6-pentyl
Methyl 4-isopropylanthranilate	7-isopropyl-
Methyl 6-chloroanthranilate	5-chloro-
Methyl 3-chloroanthranilate	8-chloro-
Ethyl 3-fluoroanthranilate	8-fluoro-
5-methylanthranilic acid	6-methyl-
6-methylanthranilic acid	5-methyl-
3-methylanthranilic acid	8-methyl-
5-nitroanthranilic acid	6-nitro-
6-nitroanthranilic acid	5-nitro-
3-amino-p-tolunitrile	7-methyl-
2-amino-4,5-dichlorobenzoic acid	6,7-dichloro-
2-aminopiperonylic acid	6,7-methylenedioxy-
2-amino-4,5-ethylenedioxybenzoic acid	6,7-ethylenedioxy-
2-naphthylamine-3-carboxylic acid	6,7-benzo-
4,5-dimethylanthranilic acid	6,7-dimethyl
4,5,6-trimethoxyanthranilic acid	5,6,7-trimethoxy

These compounds are effective hypotensive agents whose activities are similar to those in the previous examples. In addition, compounds selected from the group having the formula:



wherein R_5, R_6 and Z are as previously described are also effective hypotensive agents. The compounds of this example are prepared according to the procedures of the preceding examples. They are used in the same manner with regard to dosage level and dosage form as the compounds in the previous examples. A specific example of the preparation of this type of compound is as follows:



2-dimethylamino-4-amino-6,7-benzoquinazoline

To 8 grams of 2,4-dichloro-6,7-benzoquinazoline, prepared according to the procedure of F. H. S. Curd et al. in the Journal of the Chemical Society (London), 1948, p. 1761, is added 100 ml. of a 25% solution of anhydrous ammonia in tetrahydrofuran. The reaction mixture is stirred for 44 hours. The precipitate is filtered and recrystallized from methanol. To the product is added 100 ml. of a 25% solution of dimethylamine in ethanol. The mixture is heated in a sealed pressure bottle for 16 hours at 160° C. The solvent is evaporated and the product is recrystallized from methanol/water.

EXAMPLE LVII

4-(4-amino-6,7-dimethoxyquinazoline-2-yl)-piperazine-1-carboxylic acid isobutyl ester

Preparation of isobutyl 1-piperazinecarboxylate.—To 11.6 grams of anhydrous piperazine in 127 ml. ethanol and 16 ml. water is added with stirring over a 30 minute period, 22.6 grams 48% aqueous hydrobromic acid. The temperature rises to 60° C. during the addition. Isobutyl chloroformate (875 grams) is then added over another 30 minute period and the resulting solution is refluxed for 1.5 hours and chilled. The piperazine dihydrobromide which crystallizes is filtered and the solution is concentrated to an oil in vacuo. The oil is taken up in water, neutralized with dilute aqueous sodium hydroxide and extracted with several portions of methylene chloride. The combined extracts are dried with sodium sulfate and the methylene chloride is evaporated to yield 9.9 grams of an oil which is distilled in vacuo, B.P. 87–90° C./0.3 mm. Hg pressure. The yield of colorless product is 7.17 grams or 60% of theory.

This same procedure is used to prepare 1-(2-furoyl)-piperazine, 1 - allylpiperazine, 1 - (2 - methylallyl) - piperazine, 1 - crotonyl - piperazine, propyl - 1 - piperazinecarboxylate, allyl 1 - piperazinecarboxylate, and n - pentyl-1-piperazinecarboxylate.

Preparation of quinazoline derivative of isobutyl 1-piperazinecarboxylate.—A mixture of 7.17 grams of 2-chloro - 4 - amino - 6,7 - dimethoxyquinazoline and 11.7 grams of isobutyl 1 - piperazinecarboxylate in 80 ml. of ethanol is heated in a pressure bomb at 140° C. for 4 hours. The reaction mixture is cooled and the solvent evaporated. The resulting residue is triturated with 300 ml. water. The insoluble material is filtered from the water and dissolved in 50 ml. methanol. The methanol is displaced with 50 ml. of ethyl acetate and the product is precipitated and collected by filtration. The product is dissolved in warm ethanol-1 N hydrochloric acid and chilled. The crystals of the resulting hydrochloride are filtered from the solvent and dried to yield 8.1 grams of product (62% of theory) melting at 277–278° C.

Analysis.—Calcd. for $C_{19}H_{27}O_4N_5HCl\frac{1}{2}H_2O$ (percent): C, 52.47; H, 6.72; N, 16.12; Cl, 8.15. Found (percent): C, 52.69; H, 6.86; N, 16.23; Cl, 7.86.

EXAMPLE LVIII

2-(4-allyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline

To 18.9 grams of 2-chloro-4-amino-6,7-dimethoxyquinazoline in 280 ml. of isoamyl alcohol is added 19.9 grams of 1-allylpiperazine prepared as in Example LVII. The mixture is refluxed for 20 hours, and cooled. The 1-allylpiperazine hydrochloride formed is extracted with water and the organic layer is concentrated in vacuo to an oil which crystallizes when triturated with hexane. The solids are collected by filtration and dried to give 20.4 grams of product, M.P. 198–201° C.

The hydrochloride salt is prepared by redissolving the product in ethanol/1 N hydrochloric acid and chilling. The resulting crystals, when dried melt at 282–283° C.

EXAMPLE LIX

2-(4-benzylpiperidino)-4-amino-6,7-dimethoxyquinazoline

To 7.17 grams of 2-chloro-4-amino-6,7-dimethoxyquinazoline in ethanol is added 10.5 grams 4-benzylpiperidine. The mixture is heated in a pressure bottle for 4 hours at 140° C. The mixture is cooled, the solvent is evaporated and the residue is redissolved in methanol-chloroform (1:1). This solvent is displaced with ethyl acetate causing crystallization of product. The crystals collected weigh 6.8 grams, M.P. 260–262° C.

Analysis.—Calcd. for $C_{22}H_{26}O_2N_4HCl$ (percent): C, 63.68; H, 6.56; N, 13.50; Cl, 8.55. Found (percent): C, 63.76; H, 6.58; N, 13.72; Cl, 8.43.

EXAMPLE LX

4-(4-amino-6,7-dimethoxyquinazoline-2-yl)-piperazine-1-carboxylic acid ethyl ester hydrochloride

This compound is prepared from ethyl 1-piperazinecarboxylate and 2-chloro-4-amino-6,7-dimethoxy quinazoline according to the procedure of Example LVII.

Analysis.—Calcd. for $C_{17}H_{23}O_4N_5HCl\frac{1}{2}H_2O$ (percent): C, 50.19; H, 6.19; N, 17.22; Cl, 8.71. Found (percent): C, 49.78; H, 6.15; N, 17.11; Cl, 8.70. M.P. 277–278° C.

EXAMPLE LXI

4-(4-amino-6,7-dimethoxyquinazoline-2-yl)-piperazine-1-carboxylic acid allyl ester hydrochloride

This compound is prepared from allyl 1-piperazinecarboxylate and 2-chloro-4-amino-6,7-dimethoxyquinazoline according to the procedure of Example LVII, The hydrochloride melts at 260–262° C.

EXAMPLE LXII

2[4-(p-hydroxyethyl)-piperidino]-4-amino-6,7-dimethoxyquinazoline hydrochloride

This compound is prepared according to the procedure of Example XXIX from 2-chloro-4-amino-6,7-dimethoxyquinazoline and 1-p-hydroxyethylpiperidine. The hydrochloride salt is prepared according to the procedure of Example III. The compound melts at 239–240° C.

Analysis.—Calcd. for $C_{17}H_{24}O_3N_4HCl\frac{1}{2}H_2O$ (percent): C, 54.04; H, 6.93; N, 14.83; Cl, 9.38. Found (percent): C, 54.36; H, 7.11; N, 14.95; Cl, 9.22.

EXAMPLE LXIII

2-(4-n-propylpiperidino)-4-amino-6,7-dimethoxyquinazoline hydrochloride

This compound is prepared from 2-chloro-4-amino-6,7-dimethoxyquinazoline and 4-n-propylpiperidine ac-

cording to the procedures of Examples XXIX and III. The free base melts at 150–151° C. The hydrochloride melts at 246–247° C.

Analysis.—Calcd. for $C_{18}H_{26}O_2N_4$ (percent): C, 65.43; H, 7.92; N, 16.95. Found (percent): C, 65.23; H, 7.90; N, 16.84.

Analysis.—Calcd. for $C_{18}H_{26}O_2N_4HCl½H_2O$ (percent): C, 57.51; H, 7.51; N, 14.91; Cl, 9.43. Found (percent): C, 57.70; H, 7.59; N, 14.94; Cl, 9.70.

EXAMPLE LXIV

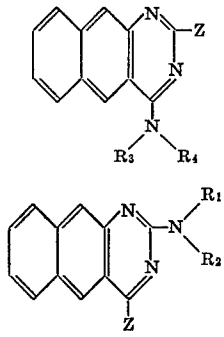
2-(4-n-heptanoyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline hydrochloride

This compound is prepared from 2-chloro-4-amino-6,7-dimethoxyquinazoline and 1-n-heptanoylpiperazine according to the procedure of Examples XXIX and III. The product melts at 155–162° C.

Analysis.—Calcd. for $C_{21}H_{31}O_3N_5HCl½H_2O$ (percent): C, 56.44; H, 7.44; N, 15.67; Cl, 7.93. Found (percent): C, 56.31; H, 7.62, N, 15.34; Cl, 7.34.

EXAMPLE LXV

The 2,4-disubstituted-6,7-benzoquinazolines of the formulae:



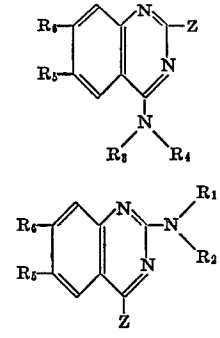
are prepared from 2,4-dichloro-6,7-benzoquinazoline, as described in Example LVI, and by the procedures of Examples XIX, XXII, XXIX, XXX, XXVIII and XXXV. These compounds are listed in Table XX.

TABLE XX

R_1 or R_3	R_2 or R_4	Z
H—	H—	piperidino
H—	H—	morpholino
H—	H—	4-methyl-1-piperidino
H—	H—	4-pentyl-1-piperidino
CH=CH—CH_2—	H—	3-oxo-piperazinyl
CH_2=CH—CH_2—	H—	4-acetyl-1-piperazinyl
CH_2=CH—CH_2—	H—	4-benzoyl-1-piperazinyl
CH_2=CH—CH_2—	H—	4-carbamoyl-1-piperazinyl
C_6H_5—	C_6H_5—	4-ethylcarbamoyl-1-piperazinyl-
C_6H_5—	C_6H_5—	4-methylcarbamoyl-1-piperazinyl-
C_6H_5—	C_6H_5—	4-diethylcarbamoyl-1-piperazinyl-
C_6H_5—	C_6H_5—	4-n-propylcarbamoyl-1-piperazinyl-
C_6H_5—	C_6H_5—CH_2—	4-dimethylcarbamoyl-1-piperazinyl-
C_6H_5—CH_2—	C_6H_5—CH_2—	4-hydroxypiperidino
4-Cl—C_6H_4—	H—	2-butoxypiperidino
4-Cl—C_6H_4—	H—	4-butoxypiperidino
3-Br—C_6H_4—	C_6H_5—	2-methylpiperidino
2-OH—C_6H_4—	H—	4-methylpiperidino
2-OH—C_6H_4—	H—	cyclopropylamino
C_6H_5—	C_6H_5—	cyclobutylamino
CH_2=CH—CH_2—	CH_2=CH—CH_2—	cycloheptylamino
HO—CH_2—CH_2—	HO—CH_2—CH_2	2-hexylpiperidino
HO—$(CH_2)_5$—	H—	2-benzylpiperidino
2-CH_3O—C_6H_4—	H—	2-hydroxymethyl-piperidino
3-CH_3O—C_6H_4—	H—	4-hydroxymethyl-piperidino
2-C(F)$_3$—CH_2—	H—	4-acetyl-1-piperazinyl
2-C(F)$_3$—CH_2—	H—	4-caproyl-1-piperazinyl
2-C_5H_{13}—C_6H_5—	H—	4-(2-furoyl)-1-piperazinyl
4-F—C_6H_4—	H—	4-(2-methylphenyl)-1-piperazinyl
C_6H_5—	C_6H_5—	4-(2-trifluoromethyl-benzoyl)-1-piperazinyl

EXAMPLE LXVI

The 2,4-disubstituted 6(7)-methoxyquinazolines of the formulae:



are prepared by the procedures of Examples XV, XVI, XIX, XXI, XXII, XXVIII and XXXV. These compounds are listed in Table XXI.

TABLE XXI

R_1 or R_3	R_2 or R_4	R_5	R_6	Z
H—	H—	H—	CH_3O—	3-hydroxypiperidino
H—	H—	H—	CH_3O—	4-hydroxypiperidino
H—	H—	H—	CH_3O—	3-methoxypiperidino
CH_2=CH—CH_2—	H—	H—	CH_3O—	4-methoxypiperidino
CH_2=CH—CH_2—	H—	C_2H_5O—	CH_3O—	3-butoxypiperidino
CH_2=CH—CH_2—	C_2H_5	CH_3O—	CH_3O—	cyclopropylamino
CH_2=CH—CH_2—	CH_3—	CH_3O—	CH_3O—	cycloheptylamino
C_6H_5—	H—	C_2H_5O—	CH_3O—	4-butoxypiperidino
C_6H_5—	C_6H_5—	CH_3O—	H—	2-methylpiperidino
C_6H_5—CH_2—	C_6H_5—	CH_3O—	H—	4-methylpiperidino
C_6H_5—CH_2—	CH_2=CH—CH_2	CH_3O—	H—	2-hexylpiperidino
CH_2=CH—CH_2—	H—	CH_3O—	CH_3O—	2-benzylpiperidino
C_6H_5—CH_2—	H—	CH_3O—	CH_3O—	4-benzylpiperidino
C_6H_5—CH_2—	C_6H_5—CH_2—	CH_3O—	CH_3O—	2-hydroxymethylpiperidino
C_6H_5—	C_6H_5—	CH_3O—	H—	4-hydroxymethylpiperidino
2-Cl—C_6H_4—	H—	CH_3O—	CH_3O—	4-(6-hydroxyhexyl)piperidino
3-Cl—C_6H_4—	H—	CH_3O—	CH_3O—	4-(4-hydroxyhexyl)piperidino
4-Cl—C_6H_4—	H—	CH_3O—	CH_3O—	4-(2-chlorophenyl)piperidino
2-Br—C_6H_4—	H—	C_2H_5O—	CH_3O—	4-(3-bromophenyl)piperdino
2-F—C_6H_4—	H—	CH_3O—	CH_3O—	4-(4-bromophenyl)piperidino
2,4-$Cl_2C_6H_3$—	H—	CH_3O—	CH_3O—	4-acetyl-1-piperazinyl
3-HO—C_6H_4—	H—	CH_3O—	H—	4-caproyl-1-piperazinyl
4-HO—C_6H_4—	H—	CH_3O—	H—	4-hept ,noyl-1-piperazinyl
HO—CH_2—CH_2—	H—	CH_3O—	H—	4-(2-furoyl)-1-piperazinyl
HO—CH_2—CH_2—	HO—CH_2	CH_3O—	H—	4-(3-furoyl)-1-piperazinyl
2-CH_3—C_6H_4—	H—	CH_3O—	CH_3O—	4-(2-thiophenoyl)-1-piperazinyl
3-CH_3—C_6H_4—	H—	CH_3O—	CH_3O—	4-(3-thiophenoyl)-1-piperazinyl
4-CH_3—C_6H_4—	H—	CH_3O—	CH_3O—	4-(2-methylallyl)-1-piperazinyl

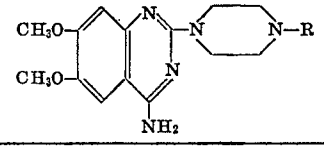
TABLE XXI—Continued

R_1 or R_3	R_2 or R_4	R_5	R_6	Z
$C_6H_5-CH_2-$	$C_6H_5-CH_2-$	CH_3O-	H—	4-(2-methoxyphenyl)-1-piperazinyl
C_6H_5-CH2-	$C_6H_5-CH_2-$	CH_3O-	H—	4-(3-methoxyphenyl)-1-piperazinyl
C_6H_5-	C_6H_5-	H—	CH_3O-	4-(4-methoxphenyl)-1-piperazinyl
C_6H_5-	C_6H_5-	H—	CH_3O-	4-(2-trifluoromethylphenyl)-1-piperazinyl
$CH_2=CH-CH_2-$	CH_3-	CH_3O-	CH_3O-	4-crotonyl-1-piperazinyl
$CH_2=CH-CH_2-$	C_2H_5-	CH_3O-	CH_3O-	cyclohexylamino
$C_6H_5-CH_2-$	H—	CH_3O-	CH_3O-	4-(3-trifluoromethylphenyl)-1-piperazinyl
$C_6H_5-CH_2-$	H—	CH_3O-	CH_3O-	4-(4-trifluoromethylphenyl)-1-piperazinyl
$2-CH_3-C_6H_4-$	H—	CH_3O-	CH_3O-	4-(2-methylphenyl)-1-piperazinyl
$3-CH_3-C_6H_4-$	H—	CH_3O-	CH_3O-	4-(3-methylphenyl)-1-piperazinyl
$4-CH_3-C_6H_4-$	H—	CH_3O-	CH_3O-	4-(4-methylphenyl)-1-piperazinyl
C_6H_5-	H—	CH_3O-	CH_3O-	4-(2-methylbenzoyl)-1-piperazinyl
C_6H_5-	H—	CH_3O-	CH_3O-	4-(3-methylbenzoyl)-1-piperazinyl
C_6H_5-	H—	C_2H_5O-	CH_3O-	4-(4-methylbenzoyl)-1-piperazinyl
C_6H_5-	H—	C_2H_5O-	CH_3O-	4-(2-trifluoromethylbenzoyl)-1-piperazinyl
C_6H_5-	C_6H_5-	C_2H_5O-	CH_3O-	4-(3-trifluoromethylbenzoyl)-1-piperazinyl
C_6H_5-	C_6H_5-	CH_3O-	H—	4-(4-trifluoromethylbenzoyl)-1-piperazinyl
$CH_2=CH-CH_2-$	H—	CH_3O-	H—	4-(2-methoxybenzoyl)-1-piperazinyl
$CH_2=CH-CH_2-$	H—	CH_3O-	H—	4-(3-methoxybenzoyl)-1-piperazinyl
$CH_2=CH-CH_2-$	H—	CH_3O-	H—	4-(4-methoxybenzoyl)-1-piperazinyl
C_6H_5-	H—	CH_3O-	CH_3O-	4-carbamoyl-1-piperazinyl
C_6H_5-	H—	CH_3O-	CH_3O-	4-methylcarbamoyl-1-piperazinyl
$C_6H_5-CH_2-$	H—	CH_3O-	CH_3O-	4-ethylcarbamoyl-1-piperazinyl
$C_6H_5-CH_2-$	$C_6H_5-CH_2-$	CH_3O-	CH_3O-	4-n-propylcarbamoyl-1-piperazinyl
$C_6H_5-CH_2-$	H—	CH_3O-	CH_3O-	4-diethylcarbamoyl-1-piperazinyl
C_6H_5-	H—	CH_3O-	CH_3O-	4-di-n-propylcarbamoyl-1-piperazinyl
C_6H_5	C_6H_5-	CH_3O-	CH_3O-	4-dimethylpropylcarbamoyl-1-piperazinyl

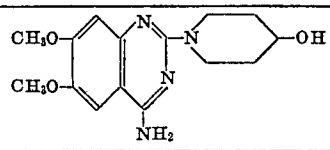
EXAMPLE LXVII

The biological activity of the compounds of this invention was tested according to the procedure of Example L. The activity of the compounds is given in Table XVIII of Example L and Table XXII.

TABLE XXII.—HYPOTENSIVE ACTIVITY



R	Minimum Effective Concentration, mg./kg.
$CH_2=C(CH_3)-CH_2-$	1.25
$C_2H_5O-C(=O)-$	0.075
$CH_3-CH(-O-C(=O)-)-CH_2-$	1.25
$CH_3-CH(CH_3)-CH_2-O-C(=O)-$	0.075



	Minimum Effective Concentration, mg./kg.
2-(4-hydroxy-1-piperidino)-4-amino-6,7-dimethoxyquinazoline	1.25

EXAMPLE LXVIII

2-diethylamino-4-chloro-6,7-dimethoxyquinazoline

A mixture of 10 grams 2-diethylamino-6,7-dimethoxy-4(3H)-quinazolene hydrochloride in 50 ml. of phosphorous oxychloride is refluxed for 2 hours. The liquids are evaporated to give a crystalline residue of 2-diethylamino-4-chloro - 6,7 - dimethoxyquinazoline hydrochloride, M.P. 175–184° C. The product is dissolved in dilute sodium hydrogen carbonate aqueous solution and is extracted several times with chloroform. The combined chloroform extracts are dried with sodium sulfate and the solvent is evaporated to yield 7.6 grams (82% of theory) of product, M.P. 129–151° C.

Analysis.—Calcd. for $C_{14}H_{18}O_2H_3$ HCl. (percent): C, 56.86; H, 6.13; N, 14.21. Found (percent): C, 56.81; H, 6.08; N, 13.97.

EXAMPLE LXIX

2-diethylamino-4-amino-6,7-dimethoxyquinazoline

The product of Example LXVIII is dissolved in 100 ml. tetrahydrofuran and a solution of anhydrous ammonia in tetrahydrofuran is added. The mixture is stirred at room temperature for 24 hours and the resulting precipitate is collected. The product is recrystallized from isopropyl alcohol. The dried product melts at 179–180° C.

EXAMPLE LXX

2-(4-allyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline

To 10 grams of 6,7-dimethoxy-(1H,3H)-quinazolinedione in 200 ml. pyridine is added 30 grams phosphorous pentasulfide and the mixture is refluxed with continuous stirring for 5 hours. The solvent is removed under reduced pressure and the residue is decomposed with hot water. The solid material is filtered from the mixture. The product is 6,7-dimethoxy-(1H,3H) - quinazolinedithione.

To 0.1 mole of 6,7-dimethoxy-(1H,3H)-quinazolinedithione in 220 ml. 1 N potassium hydroxide solution and 100 ml. methanol, is added slowly with stirring, 0.22 mole of methyl iodide. The mixture is heated on a steam bath for 2 hours, cooled, and the resulting precipitate is filtered from the mixture. The product is 2,4-dimethylmercapto-4-amino-6,7-dimethoxyquinazoline.

To 0.1 mole of 2,4-dimethylmercapto-6,7-dimethoxyquinazoline in 200 ml. of tetrahydrofuran is added a solution of 0.1 mole of anhydrous ammonia in tetrahydrofuran. The mixture is stirred at room temperature for 18 hours and the precipitate which forms is collected and recrystallized from dimethylformamide/water to yield 2-methylmercapto-4-amino-6,7 - dimethoxyquinazoline.

A mixture of 0.1 mole of 2-methylmercapto-4-amino-6,7-dimethoxyquinazoline and 0.12 mole of 1-allylpiperazine is isoamyl alcohol is heated at reflux for 13 hours. The reaction mixture is cooled, washed with water, and the organic layer is concentrated in vacuo. Hexane is slowly added to the oily residue and the solids which form are collected. The product is 2-(4-allyl-1-piper-

azinyl)-4-amino - 6,7 - dimethoxyquinazoline, M.P. 198–201° C.

EXAMPLE LXXI

2-(4-allyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline

To 0.10 mole of 2-(1-piperazinyl) - 4 - amino-6,7-dimethoxyquinazoline in 300 ml. of methanol at 50° C. is added with vigorous stirring 0.10 mole allyl bromide. The mixture is heated at reflux for 2 hours, cooled, and the crystalline material is filtered. Recrystallization from ethanol yields the desired product.

EXAMPLE LXXII

2-[4-(2-furoyl)-piperazine-yl]-4-amino-6,7-dimethoxyquinazoline

To 0.10 mole 2 - (1 - piperazinyl) - 4 - amino-6,7-dimethoxyquinazoline in 300 ml. methanol is added with vigorous stirring, 0.10 mole 2-furoyl chloride. After addition is complete, the mixture is stirred for 3 hours at room temperature. The solids are filtered to give the desired product, M.P. 278–280° C.

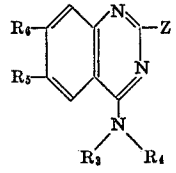
EXAMPLE LXXIII

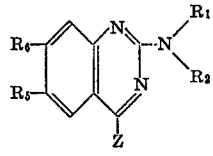
2-diethylamino-4-amino-6,7-dimethoxyquinazoline

To 0.1 mole 2-amino-4,5-dimethoxybenzonitrile in dimethylformamide is added 0.5 mole of N,N-diethylguanidine. The mixture is heated for 12 hours at 150° C. The solution is concentrated to a small volume, in vacuo. Water is added and the mixture is chilled. The solids which crystallize are filtered from the mixture and recrystallized from iso-propyl alcohol to give the desired product.

EXAMPLE LXXIV

The 2,4 - disubstituted - 6,7 - alkylquinazolines of the formula:





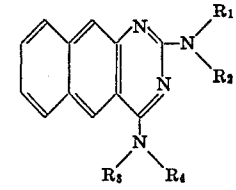
where R_5 and R_6 are methyl, ethyl, n-propyl and iso-propyl and where Z is as indicated in Table XXIII, are prepared by the procedures of Examples XV, XVI, XIX, XXI, XXII, XXVIII and XXXV. These compounds are listed in Table XXIII.

TABLE XXIII

R_1 or R_3	R_2 or R_4	R_5	R_6	Z
H—	H—	H—	CH_3—	cyclopropylamino-
H—	H—	CH_3—	CH_3—	4-crotonyl-1-piperazinyl-
H—	H—	CH_3—	H—	3-hydroxypiperidino-
H—	CH_3—	C_2H_5	H—	3-methoxypiperidino-
H—	C_2H_5—	H—	C_2H_5—	3-n-propoxypiperidino-
H—	n-C_3H_7—	n-C_3H_7—	CH_3	3-n-butoxypiperidino-
H—	H—	n-C_3H_7—	n-C_3H_7—	3-hydroxymethylpiperidino-
CH_3—	H—	iso-C_3H_7—	iso-C_3H_7—	3-hydroxyhexylpiperidino-
CH_3—	CH_3—	C_2H_5—	C_2H_5—	cyclopropylamino-
n-C_3H_7—	n-C_3H_7—	CH_3—	H—	piperidino-
CH≡C—CH_2—	CH_3—	CH_3—	CH_3—	piperidino-
CH_2=CH—CH_2—	CH_2=CH—CH_2—	CH_3—	CH_3—	4-(3-furoyl)-1-piperazinyl-
CH_2=CH—CH_2—	CH_2=CH—CH_2—	CH_3—	CH_3—	4-crotonyl-1-piperazinyl-

EXAMPLE LXXV

The 2,4-disubstituted - 6,7 - benzoquinazolines of the formula:



are prepared from 2,4-dichloro-6,7-benzoquinazoline, as described in Example LVI and by the procedures of Examples XIX, XXII, XXIX, XXX, XXVIII and XXV. These compounds are listed in Table XXIV.

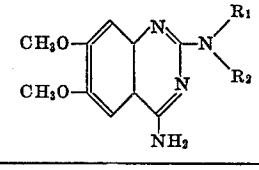
TABLE XXIV

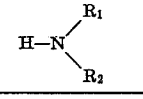
R_1	R_2	R_3	R_4
H—	H—	H—	H—
CH_3—	H—	H—	H—
CH_3—	CH_3—	CH_3—	H—
CH_3—	H—	CH_3—	CH_3—
C_2H_5—	H—	C_2H_5—	CH_3—
n-C_3H_7—	H—	n-C_3H_7—	H—
n-C_3H_7—	n-C_3H_7—	n-C_3H_7—	n-C_3H_7—
iso-C_3H_7—	iso-C_3H_7—	H—	H—
CH_2=CH—CH_2—	H—	CH_2=CH—CH_2—	H—
CH≡C—CH_2—	H—	CH_3—	H—
CH≡C—CH_2—	CH_3—	H—	H—
CH≡C—CH_2—	C_2H_5—	H—	H—
C_6H_5—	H—	CH≡C—CH_2—	H—
C_6H_5—CH_2—	H—	C_6H_5—	H—
HO—CH_2—CH_2—	H—	HO—CH_2—CH_2—	H—
4-Cl—C_6H_4—	H—	C_6H_5—	H—
3-Br—C_6H_4—	H—	4-Cl—C_6H_4—	H—
CH_3—	H—	2-CH_3O—C_6H_4—	C_6H_5—
C_2H_5—	H—	3-CH_3O—C_6H_4—	CH_3—
C_6H_5—	CH_3—	2-CH_3—C_6H_4—	H—
4-F—C_6H_4—	H—	CH_3—	CH_3—
4-HO—C_6H_4—	H—	H—	H—
C_2H_5—	CH_3—	3-CH_3—C_6H_4—	H—

EXAMPLE LXXVI

The 2,4 - disubstituted - 6,7 - dimethoxyquinazolines of Table XXV are prepared according to the procedures of Examples I and XXXVII substituting the appropriate amine for diethylamine.

TABLE XXV





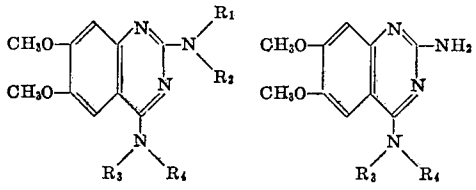
M.P., ° C.

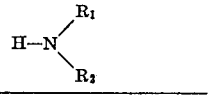
R_1	R_2	Base	2.HCl
C_2H_5	$CH_2CH_2N(CH_3)_2$	245–247	239–240
C_2H_5	$CH_2CH_2N(C_2H_5)_2$	----------	237–238
CH_3	$CH_2CH_2N(C_2H_5)_2$	261–264	262–264
H	$CH_2CH_2CH_2N(C_2H_5)_2$	235–236	260–260
H	$CH_2CH_2CH_2N(CH_3)_2$	279–280	268–269
CH_3	$CH_2CH_2CH_2N(C_2H_5)_2$	102–104	255–256
H	$CH_2CH_2CH_2NHCH(CH_3)_2$	296	303–304
H	$CH(CH_3)CH_2CH_2CH_2N(C_2H_5)_2$	185–187	231–233

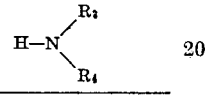
EXAMPLE LXXVII

The 2,4 - disubstituted - 6,7 - dimethoxyquinazolines of Table XXVI are prepared according to the procedure of Examples XL, XLII and LXXX by substituting the appropriate amine.

TABLE XXVI





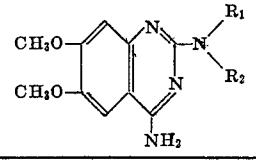


R_1	R_2	R_3	R_4
CH_3	$CH_2CH_2N(CH_3)_2$	CH_3	$CH_2CH_2N(CH_3)_2$
H	$CH_2CH_2NHCH_3$	H	$CH_2CH_2NH(CH_2)_2$
C_2H_5	$CH_2CH_2N(CH_3)_2$	C_2H_5	$CH_2CH_2NHCH_3$
C_3H_7	$CH_2CH_2CH_2N(C_2H_5)_2$	H	$CH_2CH_2N(CH_3)_2$
H	$CH_2CH_2CH_2CH_2CH_2N(CH_3)_2$	C_3H_7	$CH_2CH_2NHCH_3$
H	$CH_2CH_2NHC_3H_7$	H	$CH_2CH_2N(C_2H_5)_2$

EXAMPLE LXXVIII

The biological activity of the compounds of this invention, particularly in regard to their effectiveness in reducing blood pressure in hypertensive subjects, is illustrated by the following tests on renal hypertensive dogs. The compounds were administered orally in capsule form. The effective dose level was that which lowered the blood pressure from 180/100 to 160/100 mm. Hg. The activity of the compounds is shown in Table XXVII.

TABLE XXVII.—HYPOTENSIVE ACTIVITY



R_1	R_2	Minimum Effective Concentration, mg./kg.
H—	$—CH_2—CH_2—N(C_2H_5)_2$	10
C_2H_5—	$—CH_2—CH_2—N(CH_3)_2$	40
C_2H_5—	$—CH_2—CH_2—N(C_2H_5)_2$	10
H—	$—CH_2—CH_2—CH_2—N(CH_3)_2$	20
H—	$—CH_2—CH_2—CH_2—N(C_2H_5)_2$	10
CH_3	$—CH_2—CH_2—CH_2—N(C_2H_5)_2$	10
H	$—CH_2CH_2CH_2NHCH(CH_3)_2$	10

EXAMPLE LXXIX

2-furfurylamino-4-amino-6,7-dimethoxyquinazoline

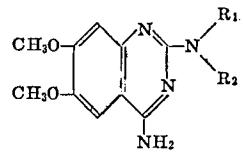
This compound is prepared according to the procedure of Example XXXVII by substituting alpha furfuryl amine for diethylamine. The product melts at 154–156° C. after recrystallization from ethyl acetate. The dihydrochloride melts at 258–260° C.

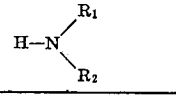
In a similar manner, 2-(N-methylfurfurylamino)-4-amino-6,7-dimethoxyquinazoline is prepared. This compound melts at 270–274° C. after recrystallization from ethanol. The dihydrochloride melts at 275–276° C.

EXAMPLE LXXX

The compounds of Table XXVIII are prepared by the procedure of Example XXXVII. Substituting the appropriate amine for diethylamine.

TABLE XXVIII



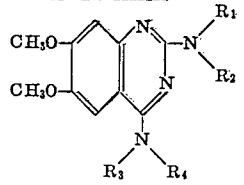


R_1	R_2
H—	$—CH_2CH_2$ 
CH_3—	$—CH_2$ 
H—	$—CH_2$ 
H—	$—CH_2CH_2$ 
CH_3—	$—CH_2CH_2$ 
CH_3—	$—CH_2CH_2$ 

EXAMPLE LXXXI

The compounds of Table XXIX are prepared according to the procedures of Examples XL, XLII, LXXIX and LXXX.

TABLE XXIX

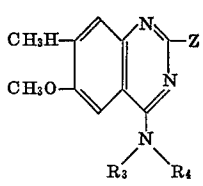


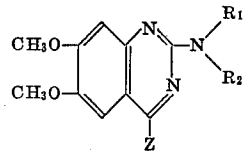
R_1	R_2	R_3	R_4
H	H	2-furfuryl	H
H	H	2-furfuryl	CH_3
H	H	2-thenyl	H
H	H	(2-thienyl)ethyl	CH_3
2-furfuryl	H	2-furfuryl	CH_3
2-thenyl	CH_3	2-furfuryl	H
2-thienyl	H	2-thenyl	CH_3
(2-furyl)ethyl	H	2-thenyl	H

EXAMPLE LXXXII

The compounds of Table XXX are prepared accord-

ing to the procedures of Examples XXII, XXX, XXIX, and LXXXI.



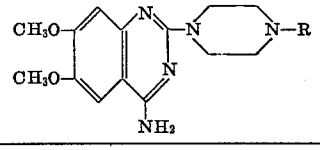
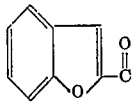
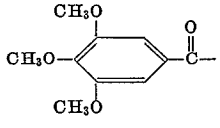
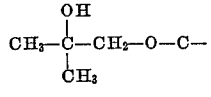
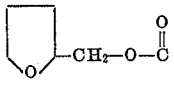
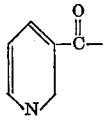
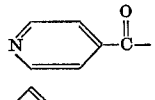
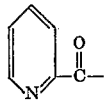
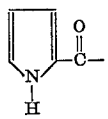
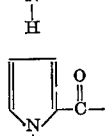
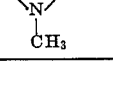


$R_1(R_3)$	$R_2(R_4)$	Z
2-furfuryl	H	morpholino
2-thenyl	H	piperazino
(2-furyl)ethyl	H	morpholino
(2-thienyl)ethyl	H	phenyl
2-furfuryl	H	4-phenylpiperidiono

EXAMPLE LXXXIII

The compounds of Table XXXI are prepared by the procedures of Examples LXXII and LVII substituting the chloride indicated.

TABLE XXXI

Chloride	Product
R–Cl ⟶	
R	
$HC\equiv C-CH_2-$	
$CH_3-C\equiv C-CH_2-$	
	
	
	
	
	
	
	
	
	
	

EXAMPLE LXXXIV

2-chloro-4-(2-hydroxyethylamino)-6,7-dimethoxyquinazoline

To 150 ml. of tetrahydrofuran was added 7.75 grams 2,4-dichloro-6,7-dimethoxyquinazoline. To the stirred solution was added at room temperature, 5.38 ml. of 2-aminoethanol. The resulting suspension was stirred for 2 hours at room temperature and filtered to give 9.6 grams of the hydrochloride salt of 2-chloro-4-(2-hydroxyethylamino)-6,7-dimethoxyquinazoline, M.P. 210–213° C.

The free base was prepared by suspending the hydrochloride in an aqueous solution of sodium bicarbonate for 1 hour. The product, 7.25 grams (85.3% of theory) melted 249–251° C.

EXAMPLE LXXXV

2-[4-(2-furoyl)-piperazin-1-yl]-4-(2-hydroxyethylamino)-6,7-dimethoxyquinazoline

This compound was prepared by adding 100 ml. of isoamyl alcohol to 5.67 grams of the base prepared in Example LXXXIV and thereafter adding 7.21 grams of 2-furoyl-1-piperazine to the suspension. The resulting mixture was heated to reflux (132° C.) where complete solution occurred. The solution was refluxed 3 hours, chilled and filtered to yield 8.8 grams (94.5% of theory) of the hydrochloride salt, M.P. 218–225° C. Recrystallization from ethanolic HCl solution yielded 6.8 grams of product, M.P. 205–208° C.

In a similar manner, 2-[4-(3-furoyl)piperazin-1-yl]-4-(2-hydroxyethylamino)-6,7-dimethoxyquinazoline is prepared.

EXAMPLE LXXXVI

2-[4-(2-furoyl)-1-piperazinyl]-4-diacetylamino-6,7-dimethoxyquinazoline

A suspension of 9.12 grams (23.8 mmoles) of 2-[4-(2-furoyl)-1-piperazinyl]-4-amino-6,7-dimethoxyquinazoline, 175 ml. of pyridine and 175 ml. (189 grams, 1.848 moles) of acetic anhydride was heated on a stream cone to give a solution. The solution was stirred at room temperature for 16 hours and concentrated in vacuo to a crystalline residue. Recrystallization from ethyl alcohol-water gave 8.3 grams (78% of theory) of product, M.P. 230–233° C.

Analysis.—For $C_{23}H_{25}O_6N_5$ (467.47). Calcd. (percent): C, 59.09; H, 5.39; N, 14.98. Found (percent): C, 59.26; H, 5.49; N, 15.10.

EXAMPLE LXXXVII

2-diethylamino-4-acetamino-6,7-dimethoxyquinazoline

To a solution of 3.2 grams 2-diethylamino-4-amino-6,7-dimethoxyquinazoline in 25 ml. pyridine was added 25 ml. (0.264 mole) of acetic anhydride. The mixture was stirred at room temperature for 2 hours and concentrated in vacuo to a crystalline residue. Recrystallization from ethyl alcohol-water gave 3.0 grams (82% of theory) of the pure product, M.P. 237–239° C.

Analysis.—For $C_{16}H_{22}O_3N_4$ (318.37). Calcd. (percent): C, 60.36; H, 6.97; N, 17.60. Found (percent): C, 60.71; H, 6.82; N, 17.70.

EXAMPLE LXXXVIII

2-diethylamino-4-[(3-diethylamino propyl)amino]-6,7-dimethoxyquinazoline

To a suspension of 6.0 grams 2-diethylamino-4-chloro-6,7-dimethoxyquinazoline hydrochloride in 50 ml. tetrahydrofuran was added 5.62 grams 3-dimethylaminopropylamine. The resulting mixture was refluxed for 48 hours. The solution was concentrated to an oil in vacuo. Crystallization from methyl alcohol - water gave 3.7 grams (51.5% of theory) of product, M.P. 107–109° C.

Analysis.—For $C_{21}H_{35}O_2N_5+\frac{1}{2}H_2O$. (398.56). Calcd.

(percent): C, 63.29; H, 9.06; N, 17.57. Found (percent): C, 63.28; H, 8.94; N, 17.29.

EXAMPLE LXXXIX

2-[4-(4-phenyl-4-carboxylic acid ethyl ester)-1-piperidino]-4-amino-6,7-dimethoxyquinazoline

This compound is prepared by the procedure of Example XXXVII by replacing diethylamine with 4-phenyl-4-carbethoxypiperidine.

The methyl, propyl, butyl, pentyl and hexyl carboxylic acid esters of 2-[4-(4-phenyl-4-carboxylic acid)-1-piperidino] - 4 - amino-6,7-dimethoxyquinazoline are prepared by the same procedure.

EXAMPLE XCI

The biological activity of the compounds of Table XXXIII was tested according to the procedure of Example LXXVIII.

TABLE XXXIII.—HYPOTENSIVE ACTIVITY

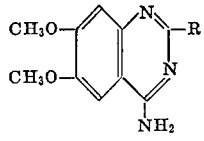
	Minimum Effective Concentration, mg./kg.
2-(4-propargyl-1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline	0.62
2-[4-(2-benzofuroyl)-1-piperazinyl]-4-amino-6,7-dimethozyquinazoline	10
2-[4-(4-phenyl-4-carboxylic acid ethyl ester)-1-piperidino]-4-amino-6,7-dimethoxyquinazoline	1.25
2-[4-(3-pyridinyl carbonyl)-1-piperazinyl]-4-amino-6,7-dimethoxyquinazoline	0.3
ethylamino-4-acetylamino-6,7-2-dimethoxyquinazoline	10
2-(4-ally-1-piperazinyl)-4-acetylamino-6,7-dimethoxyquinazoline	10
2-(4 furoyl-1-piperazinyl)-4-diacetylamino-6,7-dimethoxyquinazoline	2.5

EXAMPLE XCII

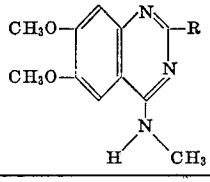
The 2,4 - disubstituted - 6,7 - dimethoxyquinazolines in Table XXXIV were given orally to dogs at the levels shown. The resulting decrease in blood pressure is indicated.

TABLE XXXIV

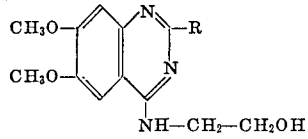
Compound



R	Blood Pressure Lowering, mm. Hg	Dose, mg./kg.
4-(3-chlorophenyl)-1-piperazinyl	25	1.25
4-(2-hydroxyethyl)-1-pipdrazinyl	20	10.0
4-(3-hydroxypropyl)-1-piperazinyl	20	10.0
4-(2-thenoyl)-1-piperazinyl	22	1.25
2-morpholinoethylamino	15	10.0



R		
Diethylamino	40	10
4-benzoyl-1-piperazinyl	30	1.25
4-allyl-1-piperazinyl	20	1.25



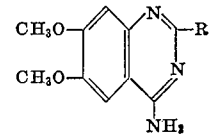
R		
4-furoyl-1-piperazinyl	30	1.25

EXAMPLE XCIII

The biological activity of the compounds of Table XXXV was tested according to the procedure of Example LXXVIII.

TABLE XXXV

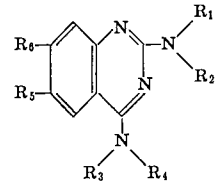
Compound



R	Minimum effective conc. (mg./kg.)
Azacyclooctyl	10.0
Azacyclohexyl	10.0
4-methylpiperidino	10.0
4-n-propylpiperidino	0.31
4-benzylpiperidino	0.31
4-phenylpiperidino	1.25
Morpholino	10.0
Cyclopropylamino	1.25
Benzylamino	10.0
4-butanoyl-1-piperazinyl	0.31
4-phenyl-1-piperazinyl	1.25
4-benzyl-1-piperazinyl	10.0
4-(3-chlorobenzoyl)-1-piperazinyl	10.0
4-(2-chlorobenzoyl)-1-piperazinyl	10.0
4-(3-methylbenzoyl)-1-piperazinyl	1.25
4-(3,4,5-trimethoxybenzoyl)-1-piperazinyl	10.0
4-(3-trifluoromethylbenzoyl)-1-piperazinyl	10.0

I claim:

1. A process for producing a hypotensive effect which comprises administering to a hypertensive host an effective amount of a compound selected from the group consisting of those having the formula:



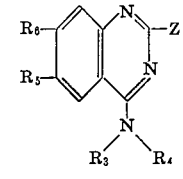
where

R_1, R_2, R_3 and R_4 are each selected from hydrogen, alkyl having from 1 to 5 carbon atoms, alkenyl having from 3 to 5 carbon atoms, hydroxyalkyl having from 2 to 5 carbon atoms, phenyl, benzyl, phenylethyl, 2-furfuryl, 2,2,2-trifluoroethyl and cycloalkyl where alkyl has from 3 to 8 carbon atoms;

R_5 and R_6 are each selected from hydrogen and alkoxy having from 1 to 3 carbon atoms, at least one of R_5 and R_6 being alkoxy; and the pharmaceutically-acceptable acid addition salts thereof.

2. The process of claim 1 wherein the administered compound is 2 - dimethylamino - 4 - amino - 6,7 - dimethoxyquinazoline.

3. A process for producing a hypotensive effect which comprises administering to a hypertensive host an effective amount of a compound selected from the group consisting of those having the formula:

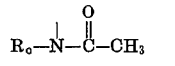


where

R_3 and R_4 are each selected from hydrogen, alkyl having from 1 to 5 carbon atoms, alkenyl having from 3 to 5

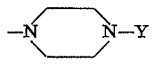
carbon atoms, hydroxyalkyl having from 2 to 5 carbon atoms, phenyl, benzyl, phenylethyl, 2-furfuryl, 2,2,2-trifluoroethyl and cycloalkyl where alkyl has from 3 to 8 carbon atoms;

Z is selected from morpholino, 1-azacycloheptyl, 1-azacyclooctyl and acetylamino of the formula:



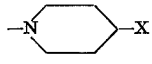
where R_0 is hydrogen, acetyl, alkyl having from 1 to 5 carbon atoms and alkenyl having from 3 to 5 carbon atoms; and

piperazino of the formula:



where Y is hydrogen, alkyl having from 1 to 5 carbon atoms, hydroxyalkyl where alkyl has from 2 to 5 carbon atoms, alkanoyl having from 2 to 7 carbon atoms, allyl, propargyl, 2-methylallyl, phenyl, benzyl, benzoyl, halobenzoyl and halophenyl where halo is chloro or bromo, trifluoromethyl, methoxyphenyl, methylphenyl, methylbenzoyl, methoxybenzoyl, trifluoromethylbenzoyl, furoyl, benzofuroyl, thenoyl, pyridinecarbonyl, 3,4,5-trimethoxybenzoyl, carboxylic acid alkyl ester where alkyl has from 1 to 6 carbon atoms, carboxylic acid alkenyl ester where alkenyl has from 3 to 6 carbon atoms; and

piperadino of the formula:



where X is hydrogen, alkyl having from 1 to 5 carbon atoms, alkoxy having from 1 to 4 carbon atoms, hydroxy, hydroxyalkyl where alkyl has from 2 to 5 carbon atoms, phenyl, benzyl, 4-phenyl-4-carboxylic acid alkyl ester where alkyl has from 1 to 6 carbon atoms;

R_5 and R_6 are each selected from hydrogen and alkoxy having from 1 to 5 carbon atoms, at least one of R_5 and R_6 being alkoxy, and the pharmaceutically-acceptable acid addition salts thereof.

4. The process of claim **3** wherein said selected compound is 2-[4-(2-furoyl) - 1 - piperazine-1-yl]-4-amino-6,7-dimethoxyquinazoline.

5. The process of claim **3** wherein said selected compound is 2-(4-allyl - 1 - piperazinyl)-amino-6,7-dimethoxyquinazoline.

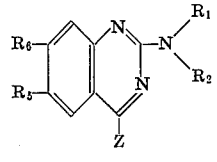
6. The process of claim **3** wherein said selected compound is 2-[4-(2-methylallyl) - 1 - piperazinyl]-4-amino-6,7-dimethoxyquinazoline.

7. The process of claim **3** wherein said selected compound is 2-(4-benzoyl - 1 - piperazinyl) - 4 - amino-6,7-dimethoxyquinazoline.

8. The process of claim **3** wherein said selected compound is 4-(4-amino - 6,7 - dimethoxyquinazoline-2-yl) piperazine-1-carboxylic acid isobutyl ester.

9. The process of claim **3** wherein said selected compound is 4-(4-amino - 6,7 - dimethoxyquinazoline-2-yl) piperazine-1-carboxylic acid ethyl ester.

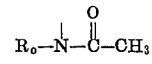
10. A process for producing a hypotensive effect which comprises administering to a hypertensive host an effective amount of a compound selected from the group consisting of those having the formula:



where

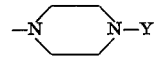
R_1 and R_2 are each selected from hydrogen, alkyl having from 1 to 5 carbon atoms, alkenyl having from 3 to 5 carbon atoms, hydroxyalkyl having from 2 to 5 carbon atoms, phenyl, benzyl, phenylethyl, 2-furfuryl, 2,2,2-trifluoroethyl and cycloalkyl where alkyl has from 3 to 8 carbon atoms;

Z is selected from morpholine, 1-azacycloheptyl, 1-azacyclooctyl and acetylamino of the formula:



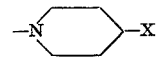
where R_0 is hydrogen, acetyl, alkyl having from 1 to 5 carbon atoms and alkenyl having from 3 to 5 carbon atoms; and

piperazino of the formula:



where Y is hydrogen, alkyl having from 1 to 5 carbon atoms, hydroxyalkyl where alkyl has from 2 to 5 carbon atoms, alkanoyl having from 2 to 7 carbon atoms, allyl, propargyl, 2-methylallyl, phenyl, benzyl, benzoyl, halobenzoyl and halophenyl where halo is chloro or bromo, trifluoromethyl, methoxyphenyl, methylphenyl, methylbenzoyl, methoxybenzoyl, trifluoromethylbenzoyl, furoyl, benzofuroyl, thenoyl, pyridinecarbonyl, 3,4,5-trimethoxybenzoyl, carboxylic acid alkyl ester where alkyl has from 1 to 6 carbon atoms, carboxylic acid alkenyl ester where alkenyl has from 3 to 6 carbon atoms; and

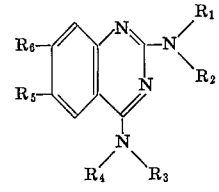
piperidino of the formula:



where X is hydrogen, alkyl having from 1 to 5 carbon atoms, alkoxy having from 1 to 5 carbon atoms, hydroxy, hydroxyalkyl where alkyl has from 2 to 5 carbon atoms, phenyl, benzyl, 4-phenyl-4-carboxylic acid alkyl ester where alkyl has from 1 to 6 carbon atoms; and

R_5 and R_6 are each selected from hydrogen and alkoxy having from 1 to 3 carbon atoms, at least one of R_5 and R_6 being alkoxy; and the pharmaceutically-acceptable acid addition salts thereof.

11. A process for producing a hypotensive effect which comprises administering to a hypertensive host an effective amount of a compound selected from those having the formula:



where

R_1 and R_3 are hydrogen or alkyl having from 1 to 3 carbon atoms;

R_2 and R_4 are hydrogen, alkyl having from 1 to 3 carbon atoms, at least one of R_2 and R_4 is dimethylaminoalkyl, diethylaminoalkyl, dipropylaminoalkyl, methylaminoalkyl, ethylaminoalkyl or propyaminoalkyl where alkyl has from 2 to 4 carbon atoms;

R_5 and R_6 are selected from hydrogen and alkoxy having from 1 to 3 carbon atoms, at least one of R_5 and R_6 being alkoxy; and the pharmaceutically-acceptable acid addition salts thereof.

References Cited

Tilford—Chem. Abst., vol. 57 (1962), p. 9824b.

SAM ROSEN, Primary Examiner

U.S. Cl. X.R.

424—248

UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,663,706 Dated May 16, 1972

Inventor(s) Hans-Jurgen E. Hess

It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

Col. 1, lines 9 and 29,"August 6, 1965" (two occurrences) should read --July 6, 1965--.

Signed and Sealed this

Twenty-first Day of *February 1984*

[SEAL]

Attest:

GERALD J. MOSSINGHOFF

Attesting Officer *Commissioner of Patents and Trademarks*