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(54) PROCESS FOR HYPOTENSIVE 2-(4-SUBSTITUTED PIPERAZIN-1-YL)-4-AMINOQUINAZOLINES

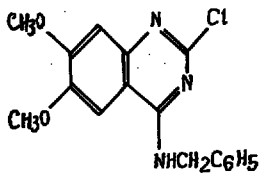
(71) We, PFIZER INC., a corporation organised under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, City of New York, State of New York, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to a new chemical process for the production of certain known chemical compounds, valuable in the art by virtue of their ability to lower blood pressure in hypertensive mammals. More specifically, these hypotensive agents are certain 2 - (4 - substituted piperazin-1-yl)-4-amino-6,7-dimethoxyquinazolines and 2 - (4 - substituted piperazin - 1 - yl) - 4 - amino - 6,7,8 - trimethoxyquinazolines, use of which is taught in United States patents 3,511,836 and 3,669,968.

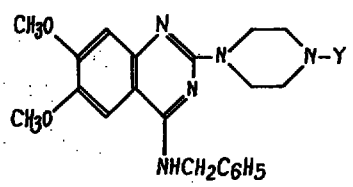
U.S. 3,511,836 which is equivalent to British Patent Specification 1,156,973 discloses several processes for the preparation of 2-(4-substituted piperazin-1-yl)-4-amino-6,7-dimethoxyquinazolines. For example, by the reaction of 2-chloro-4-amino-6,7-dimethoxyquinazoline with the appropriate 1-substituted piperazine, by reaction of a 2 - (4 - substituted piperazin - 1 - yl) - 4 - chloro - 6,7 - dimethoxyquinazoline with ammonia or by alkylation, alkanoylation, aroylation or alkoxylation of 2-(1-piperazinyl)-4-amino-6,7-dimethoxyquinazoline. U.S. 3,669,968 which is equivalent to British Patent Specification 1,309,835 teaches the preparation of 2-(4-substituted piperazin-1-yl)-4-amino-6,7,8-trimethoxyquinazolines *via* reaction of 2-chloro-4-amino-6,7,8-trimethoxyquinazoline with the appropriate 1-substituted piperazine.

In U.S. 3,935,213 processes are disclosed whereby 2-(4-substituted piperazin-1-yl)-4-amino-6,7-dimethoxyquinazolines and the corresponding 6,7,8-trimethoxyquinazolines are produced by either: (1) reaction of the appropriate 4,5-dimethoxy substituted or 3,4,5-trimethoxy-substituted 2-aminobenzonitrile with certain 1,4-disubstituted piperazines; or (2) reaction of the appropriate 4,5-dimethoxy or 3,4,5-trimethoxy substituted 2-aminobenzamidine with the same 1,4-disubstituted piperazines.

Compounds of the formulae



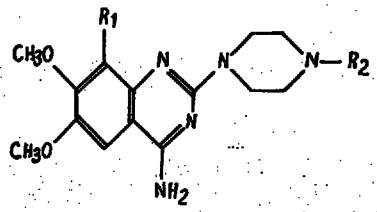
and



where Y is hydrogen, alkyl having from 1 to 5 carbon atoms, hydroxyalkyl having from 2 to 5 carbon atoms, alkanoyl having 2 to 7 carbon atoms, allyl, propargyl, 2-methallyl, phenyl, benzyl, benzoyl, and halobenzoyl where halo is chloro or bromo, trifluoromethyl, methoxyphenyl, methylphenyl, methylbenzoyl, trifluoromethylbenzoyl, furoyl,

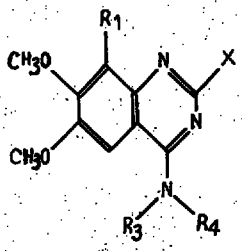
benzofuroyl, thenoyl, pyridinecarbonyl, 3,4,5-trimethoxybenzoyl, carboxylic acid alkyl ester where alkyl has from 1 to 6 carbon atoms and carboxylic acid alkenyl ester where alkenyl has from 3 to 6 carbon atoms, are disclosed in U.S. 3,511,836.

The invention relates to a novel process for preparing a final product of formula (I)



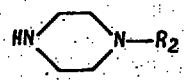
----(I)

or a hydrochloride or hydrobromide salt thereof, which comprises reacting one mole of a first reactant of formula (II).



----(II)

with from one to two moles of a second reactant of formula (III)



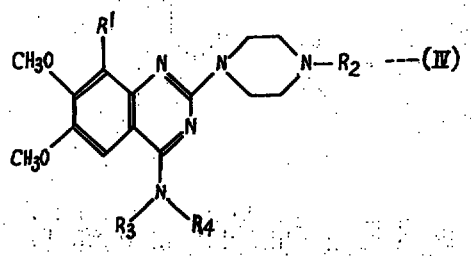
---(III)

in a reaction inert organic solvent at a temperature from 50° to 200°C.; and if necessary, thereafter removing the amino-protecting group wherein X is Cl or Br; R_1 is hydrogen or methoxy; R_2 is alkenyl having from three to five carbon atoms, benzoyl, furoyl, thienylcarbonyl, alkoxycarbonyl having from two to five carbon atoms, alkenyloxycarbonyl having from four to five carbon atoms or (2-hydroxyalkoxy)carbonyl having from four to five carbon atoms; when taken separately, R_3 is hydrogen and R_4 is $—CH_2C_6H_4R_5$, $—COOCH_2C_6H_4R_5$, $—COR_6$, $—COCF_3$, —CHO or $—COOR_6$, and when taken together with the nitrogen atom to which they are attached, R_3 and R_4 form a phthalimido, maleimido or succinimido group;

R_5 is hydrogen, chloro, bromo, methyl, methoxy or nitro; R_6 is an alkyl group having from one to four carbon atoms or $—C_6H_4R_5$.

An especially preferred range of temperature is from 80° to 130°C.

When the above process is carried out with reactants (II) and (III) wherein R_2 is benzoyl, furoyl, thienylcarbonyl, alkoxycarbonyl having from two to five carbon atoms or (2-hydroxyalkoxy)carbonyl having from four to five carbon atoms; R_3 is hydrogen and R_4 is $—CH_2C_6H_4R_5$ it is preferred to react equimolar amounts of said reactants. An intermediate of formula (IV) or a hydrochloride or hydrobromide salt thereof is obtained and said intermediate



---(IV)

is further reacted by catalytic hydrogenolysis to form said final product of formula (I). An especially preferred catalyst for said hydrogenolysis is palladium.

When the process of the invention is carried out with a first reactant of formula (II) wherein R_8 and R_4 taken together with the nitrogen atom to which they are attached form a phthalimido, maleimido or succinimido group, it is also preferred to employ equimolar amounts of said reactants to form an intermediate of formula (IV) or a hydrochloride or hydrobromide salt thereof. In which case, said intermediate is further reacted at a temperature from 0° to 100°C. to form said final product of formula (I) by

a. hydrolysis, or

b. reaction with an equimolar amount of hydrazine in the presence of a reaction inert organic solvent.

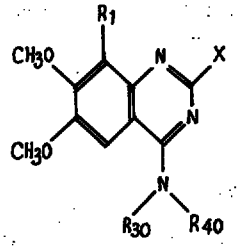
An especially preferred temperature for further reacting the above intermediates of formula (IV) by hydrolysis or with hydrazine is from 20° to 50°C.

When said hydrolysis is employed it is preferred that it be carried out using hydrochloric, hydrobromic, sulfuric or phosphoric acid.

When the process of the invention is carried out with compounds of formula (II) wherein R_8 is hydrogen and R_4 is $—COOCH_2C_6H_4R_5$, $—COR_6$, $—COCF_3$, —CHO or $—COOR_6$ wherein R_5 and R_6 are as previously defined, the desired compounds of formula (I), a hydrochloride or hydrobromide addition salt thereof, are directly provided. In the latter case one mole of said first reactant of formula (II) is reacted with two moles of said second reactant of formula (III).

Whereas the process is useful for the preparation of the said, known, hypotensive agents of Formula I, it is especially useful in the preparation of two particularly valuable members of this group of congeners; namely, 2-[4-(2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline and 2 - [4 - (2 - hydroxy - 2 - methylprop - 1 - yloxycarbonyl) - piperazin - 1 - yl] - 4 - amino - 6,7,8 - trimethoxyquinazoline, known in the art as prazosin and trimazosin. 2-[4-(2-methylprop-2-enyloxycarbonyl)piperazin-1-yl]-4-amino-6,7,8-trimethoxyquinazoline is a valuable starting material for production of trimazosin (United States Patent No. 3,669,968). Prazosin and trimazosin have recently been reported to have therapeutic utility in man (Cohen, *Journal of Clinical Pharmacology, 10,* 408 [1970]; De Guia, et al., *Current Therapeutic Research, 15,* 339 [1973]).

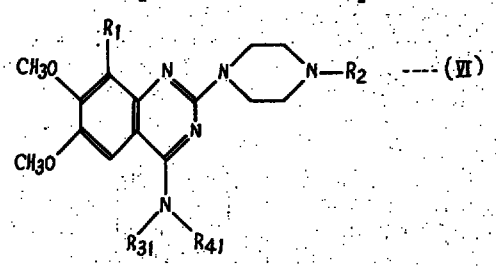
Useful intermediates in the process are the compounds of formula (V).



----(V)

wherein X and R_1 are as previously defined, and when taken separately, R_{30} is hydrogen and R_{40} is $—COOCH_2C_6H_4R_5$, $—COR_6$, $—COCF_3$, —CHO or $—COOR_6$ and when taken together with the nitrogen atom to which they are attached R_{30} and R_{40} form a phthalimido, maleimido or succinimido group; R_5 and R_6 are as defined above.

Also useful as intermediates in the process are the compounds of formula (VI)



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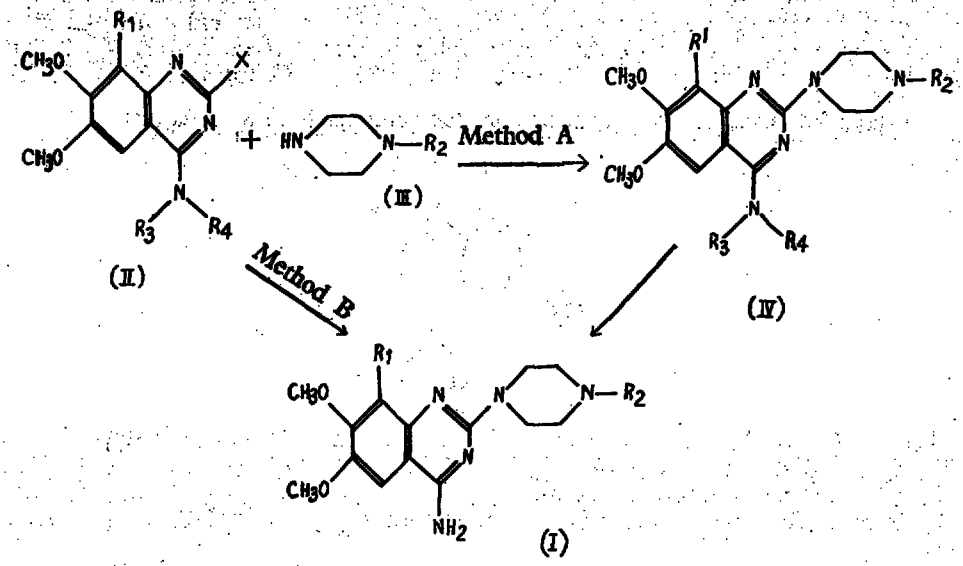
wherein R_1 and R_2 are as previously defined and R_{31} and R_{41} when taken together with the nitrogen atom to which they are attached form a phthalimido, maleimido or succinimido group.

It is an object of the invention to provide a process for the preparation of com-

pounds of the formula (I), a hydrochloride or hydrobromide salt thereof, by reacting a compound of the formula (II) with a compound of formula (III).

In certain cases, described in detail below, an intermediate product of formula (IV), or salt thereof, is initially obtained which is further reacted to obtain compounds of formula (I). The reaction of compounds of the formulae (II) and (III) is carried out in the presence of an appropriate reaction inert organic solvent. An appropriate solvent is one which will serve to substantially dissolve the reactants, and will not adversely interact with reactants or products of the reaction. Examples of such solvents are alkanols such as isopropanol, butanol, isobutanol, isoamyl alcohol, 2-methyl-2-pentanol and 3,3-dimethyl-1-butanol; glycols such as ethylene glycol and diethylene glycol; glycol ethers such as ethyleneglycol monomethyl ether, diethylene glycol monoethyl ether, 1,2-dimethoxyethane, and diethylene glycol dimethyl ether; tertiary amides such as N,N-dimethylformamide,N,N-diethylacetamide and N-methylpyrrolidone; dimethylsulfoxide and pyridine. The reaction is carried out at a temperature in the range of 50° to 200°C. An especially preferred range of temperature is from 80° to 130°C. The time required for this process to reach substantial completion varies according to several factors, such as, for example, the reaction temperature, reactivity of the particular starting materials employed and the concentration of reactants. As will be appreciated by one skilled in the art, at lower temperatures longer reaction times are needed, while at higher temperatures the reaction is completed in a shorter time. Ordinarily, however, reaction times of from 15 minutes to 50 hours, are sufficient.

As mentioned above, in certain cases the reaction of compounds of formula (II) with compounds of formula (III) form an intermediate compound of formula (IV) which is then further reacted to obtain the desired compounds of forumla (I). Thus, the process of the invention can be carried out by either of two methods, designated as Method A and Method B, as shown in the following reaction scheme.



The compounds of formulae (II) and (III) employed as reactants in the process of the invention are those wherein X is chloro or bromo and particularly preferred as X is chloro; R_1 is hydrogen or methoxy; R_2 is alkenyl having from three to five carbon atoms, benzoyl, furoyl, thienylcarbonyl, alkoxycarbonyl having from two to five carbon atoms, alkenoxycarbonyl having from four to five carbon atoms or (2-hydroxyalkoxy)-carbonyl having from four to five carbon atoms. When taken separately, R_3 is hydrogen and R_4 is $-CH_2C_6H_4R_5$, $-COOCH_2C_6H_4R_5$, $-COR_6$, $-COCF_3$, $-CHO$ or $-COOR_6$ and when taken together with the nitrogen atom to which they are attached R_3 and R_4 form a phthalimido, succinimido or maleimido group. R_5 is hydrogen, chloro, bromo, methyl, methoxy or nitro; R_6 is alkyl having from one to four carbon atoms or $-C_6H_4R_5$.

When the process of the invention is carried out according to Method A, as depicted in the above reaction scheme, it is preferred to employ compounds of the formula (II) wherein X is chloro or bromo; R_1 is hydrogen or methoxy and when taken separately R_3 is hydrogen and R_4 is $-CH_2C_6H_4R_5$ wherein R_5 is as previously defined, and when taken together with the nitrogen atom to which they are attached, R_3 and R_4

form phthalimido, maleimido or succinimido. Such compounds of formula (II) react with the above described compounds of formula (III) to obtain intermediates of formula (IV), a hydrochloride or hydrobromide salt thereof. When such compounds of formula (IV) are desired the reaction is carried out using equimolar amounts of the reactants for reasons of economy and efficiency.

The products of formula (IV) can conveniently be isolated in the form of the hydrochloride salt or hydrobromide salt which are ordinarily insoluble in the reaction solvent and can thus be obtained merely by filtration and washing. Alternatively, the above mentioned salts can be treated during workup of the reaction mixture with an alkaline reagent such as, for example, sodium hydroxide, potassium hydroxide, potassium carbonate, or sodium methoxide, followed by extraction of the free base into a water immiscible solvent such as, for example, chloroform, dichloromethane or benzene; and evaporation to dryness. When desired, either the compounds of formula (IV) or the above mentioned salts thereof may be further purified by standard methods such as crystallization or column chromatography. However, they are often of sufficient purity for further reacting to form compounds of formula (I) without such further purification.

As mentioned above, the compounds of formula (IV) or said hydrohalide salts are further reacted to remove the 4-amino substituents, R_3 and R_4, to obtain the desired compounds of formula (I). When employing compounds of formula (IV) wherein R_3 is hydrogen and R_4 is a benzyl group, $-CH_2C_6H_4R_5$, the preferred values of R_2 are benzoyl, furoyl, thienylcarbonyl, alkoxycarbonyl having from two to five carbon atoms and (2-hydroxyalkoxy)-carbonyl having from four to five carbon atoms. It is preferred to remove said benzyl group by catalytic hydrogenolysis. The term "catalytic hydrogenolysis" as used herein is well understood by those skilled in the art of hydrogenation, and is illustrated in the examples appearing herein.

The catalytic hydrogenolysis can be carried out by a variety of procedures well known in the art for this type of transformation, such as those discussed by Augustine in "Catalytic Hydrogenation", Marcel Dekker, Inc., New York, 1965, pp. 139—142. A particularly convenient procedure comprises contacting said compound (IV), wherein R_3 is hydrogen and R_4 is $-CH_2C_6H_4R_6$, with hydrogen, in the presence of a reaction inert solvent medium and in the presence of a suitable catalyst at an appropriate temperature and pressure until hydrogenolysis is complete. Thereafter the desired product of formula (I) may be recovered by conventional methods involving catalyst removal and recovery of the product from the solvent medium.

As used herein "reaction inert solvent medium" refers to any medium which is a solvent or suitable suspending agent for the reactant, is stable under the hydrogenolysis conditions and does not interfere with the effectiveness of the catalyst or interact with the reactant or product. Polar organic solvents are generally suitable and include the C_1—C_4 alkanols such as methanol, ethanol, and butanol, cyclic and straight chain water soluble ethers such as dioxane, tetrahydrofuran, diethylene glycol monomethylether, 2-ethoxyethanol, the lower alkanoic acids such as acetic acid, propionic acid, aqueous media including the foregoing solvents and dilute aqueous hydrochloric acid. As will be appreciated, these solvents and others are conventional in known hydrogenation techniques and hence are not critical.

The temperature is no more critical than it is in other known hydrogenolyses. Thus, temperatures of from 0° to 100°C. may be employed with good results. The preferred range of temperature, however, is from 10° to 60°C. and room temperature is especially preferred for reasons of convenience. At temperatures below 0°C. the reaction is inordinately slow whereas at temperatures above 100°C., decomposition of the starting material may occur. As is to be expected, the higher the temperature, the faster the reaction rate. However, the reaction, ordinarily, is complete in 1 to 24 hours.

Suitable catalysts for obtaining the desired products of formula (I) in the hydrogenolysis reaction include platinum, palladium, rhenium, rhodium and ruthenium, either of the supported or non-supported type, as well as catalytic compounds thereof such as the oxides and chlorides. Examples of suitable catalyst supports include carbon, silica and barium sulfate. Especially preferred as catalyst is palladium for reasons of economy and efficiency.

The catalyst is ordinarily employed in an amount of from 10% to 100% by weight based on said starting material of formula (IV).

The pressure employed during hydrogenolysis is not critical, for example, satisfactory results may be obtained at pressures varying from ambient pressure to 100 atmospheres.

When employing the compounds of formula (IV) wherein R_3 and R_4 taken

together with the nitrogen atom to which they are attached form one of the above mentioned cyclic imido groups, said compounds (IV) are further reacted by hydrolysis or with hydrazine to provide the desired products of formula (I). Said hydrolysis may be carried out under alkaline conditions in the presence of, for example, sodium hydroxide or potassium hydroxide, or under acidic conditions employing a suitable acid. Examples of such suitable acids are hydrochloric, hydrobromic, sulfuric, phosphoric, hydroiodic, dichloroacetic and trifluoroacetic acids. For hydrolysis of the preferred cyclic imido compounds of formula (IV) it has been found to be particularly convenient and efficient to employ hydrochloric, hydrobromic, sulfuric or phosphoric acids. It is preferred to carry out said hydrolysis with one of these acids at a temperature in the range of 0° to 100°C., a particularly preferred range of temperature for such hydrolysis is from 20° to 50°C. At temperatures below 0°C., the hydrolysis rate is inordinately slow. At temperatures above 100°C., excessive amounts of decomposition products are generated.

The mole ratio of the above acids to compound of formula (IV) may vary over a wide range, thus mole ratios of from 1:1 to 200:1 may be employed with satisfactory results. The time required to reach substantial completion of the hydrolysis will vary according to the reaction temperature, and ordinarily when carried out at 100°C. only a few minutes is sufficient and when carried out at 0°C. up to 24 hours may be required to reach completion. The hydrolysis may be carried out in an aqueous medium or an aqueous-organic medium employing a water immiscible organic solvent such as, for example, chloroform, methylene dichloride, benzene, or toluene. Upon completion of the hydrolysis, which may be determined readily by thin-layer chromatography on silica gel employing, for example, a 95:5 ethyl acetate/diethylamine solvent system, the desired product of formula (I) may be isolated as a salt of the acid used in the hydrolysis, employing methods well known in the art. However, it is ordinarily more convenient to adjust the reaction mixture to an alkaline pH by addition of, for example, sodium hydroxide, potassium hydroxide or sodium carbonate, followed by extraction of the compound of formula (I) free base, employing, for example, one of the above mentioned organic solvents optionally employed in the hydrolysis. The product is then readily obtained by evaporation.

Alternatively, as mentioned above, the intermediates of formula (IV) wherein R_3 and R_4 when taken together with the nitrogen atom to which they are attached form one of the cyclic imido groups, may be further reacted with hydrazine to provide the final products of formula (I). The use of hydrazine to remove the phthaloyl group from phthalimido acids or the corresponding lower alkyl esters is known in the art, see, for example, Boissannas, *Advances in Org. Chem. 3*, 179—183 (1963) and Sheehan *et al., Jour. Amer. Chem. Soc., 76*, 6329 (1954). It has now been found that the above intermediates (IV) containing one of the previously mentioned cyclic imido groups also react to provide the desired products of formula (I). The reaction is carried out in the presence of a reaction inert organic solvent. Examples of organic solvents which may be employed for this reaction are the lower alkanols such as ethanol, propanol, isopropanol, butanol, and isoamyl alcohol; N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulfoxide, diethyleneglycol dimethylether and diethyleneglycol monoethylether.

The hydrazine employed may be substantially pure hydrazine or a derivative such as hydrazine hydrate, hydrazine hydrochloride or hydrazine sulfate. When the acid addition salts are employed the hydrazine is generated *in situ* by addition of a suitable base to neutralize the acid. Examples of such suitable bases are sodium methoxide, potassium carbonate, triethylamine, triethanolamine and sodium hydroxide. In this reaction, an equimolar amount of hydrazine is employed to minimize possible side reactions and for reasons of economy. It is preferred to carry out the reaction with hydrazine at temperatures from 0° to 100°C. A particularly preferred range of temperature is from 20° to 50°C. At temperatures above 100°C. unwanted side reactions occur, while at temperatures below 0°C. the reaction rate is inordinately slow.

The time required to reach substantial completion of reaction will, of course, vary with the temperature and the precise nature of the reactants and solvent. Ordinarily, however, the reaction with hydrazine to form the final product of formula (I) will be substantially complete in from 1 to 48 hours. The reaction of hydrazine with the above cyclic imido compounds also forms a cyclic hydrazide byproduct, such as, for example phthaloylhydrazide in the case of the phthalimido intermediates. The reaction mixture may be freed from the byproduct cyclic hydrazide and the desired product of formula (I) may be isolated by methods well known in the art such as, for example, evaporation *in vacuo* to dryness, trituration of the residue with dilute strong mineral acid such as hydrochloric, or sulfuric acid in which the cyclic hydrazide is usually only sparingly

soluble, filtering and adjusting the filtrate to an alkaline pH whereupon the desired product is isolated by extraction or filtration.

When compounds of the formula (II) wherein R_1 is hydrogen or methyl, R_8 is hydrogen and R_4 is $-COOCH_2C_6H_4R_5$, $-COR_6$, $-COCF_3$, $-CHO$ or $-COOR_6$ wherein R_5 and R_6 are as previously defined are reacted with 2 moles of a 1-substituted piperazines of formula (III) in the process of the invention, the reaction proceeds directly to provide the desired compounds (I) as indicated by Method B in the above reaction scheme. Thus, with such compounds of formula (II), the 1-substituted piperazines (III) react at both the 2-position of the quinazolines (II) to displace the halogen atom, X, (X=Cl or Br) and to remove the R_4 group when R_8 is hydrogen and R_4 is one of the above carbonyl containing groups, to obtain compounds of formula (I) in a single step.

When the process of the reaction is carried out according to Method B, the desired products of formula (I) are readily isolated by standard methods either in the form of the hydrochloride salt (when X is chloro), the hydrobromide salt (when X is bromo) or as the free base. For example, when a compound of the formula (II) wherein the especially preferred value of X equals chloro is reacted with two moles of a compound of formula (III), the hydrochloride salt of compound (I) is ordinarily obtained merely by filtration of the reaction mixture and washing the product. When the free base of the product of formula (I) is desired, the reaction mixture, upon completion of the reaction, is treated with an excess of an aqueous solution of a strongly alkaline reagent such as sodium hydroxide, potassium hydroxide or sodium carbonate and the free base extracted with a water immiscible solvent such as chloroform, methylene chloride, 1,2-dichloroethane and benzene. The product may then be obtained, for example, by evaporation of solvent and further purified if desired.

The following examples are provided to further illustrate the invention.

EXAMPLE 1

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

In a 200 ml. three-necked round bottomed flask was placed 6.48 g. (0.025 mole) 2,4-dichloro-6,7-dimethoxyquinazoline and 104 ml. of tetrahydrofuran. The flask was heated by means of an oil bath held at 70°C. To the flask was then added 2.68 g. (0.025 mole) of benzylamine and the resulting mixture heated with stirring for one hour. An additional charge of 2.68 g. benzylamine was added and heating continued for one hour, after which another 2.68 g. of benzylamine was added. The mixture was heated for an additional 2 hours, then filtered while still hot to remove precipitated benzylamine hydrochloride. The filtrate was concentrated to half volume, two volumes of hexane was added and the resulting mixture was stirred slowly for thirty minutes to effect granulation. Upon filtering and drying 6.0 g. (73%) of the title compound was obtained, M.P. 190—195°C. The structure was verified by means of nuclear magnetic resonance spectroscopy (NMR) and mass spectroscopy.

EXAMPLE 2

2-[4-(2-Furoyl)piperazin-1-yl]-4-benzylamino-6,7-dimethoxyquinazoline

In a 200 ml., three-necked, round bottom flask fitted with thermometer, condenser and drying tube was placed 66 ml. of isoamyl alcohol and 6.0 g. (0.018 mole) of 4-benzylamino-2-chloro-6,7-dimethoxyquinazoline. To this was added a solution of 3.6 g. (0.020 mole) 1-(2-furoyl)piperazine in 50 ml. of isoamyl alcohol. The resulting mixture was heated at reflux (130°C.) for 4 hours, cooled to 20°C., filtered, washed with ethyl ether and air dried to obtain the hydrochloride salt of the title compound. This was converted to the free base by dissolving in 150 ml. hot methanol, adding 1.3 g. of sodium methoxide, stirring at 50°C. for ten minutes, cooling to 20°C., adding 100 ml. of water, followed by extraction with two 100 ml. portions of chloroform. After concentration of the extracts to dryness 6.0 g. (70%) of the title compound. M.P. 220—225°C., was obtained.

When the above procedure is carried out at 80°C. for twenty four hours the results are substantially unchanged.

When the reaction is repeated using carbitol (diethyleneglycol monoethyl ether) as solvent and heating at either 200°C. for 20 minutes or at 50°C. for 48 hours, the title compound is similarly obtained.

EXAMPLE 3

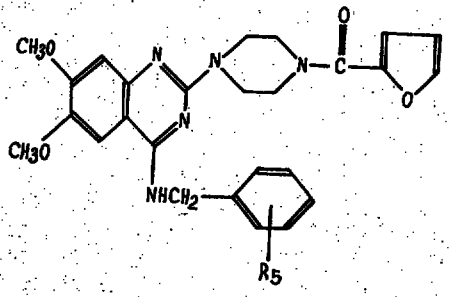
2-[4-(2-Furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline (Prazosin)

In a Parr bottle was placed 1.0 g. (2.1 millimoles) of 2-[4-(2-furoyl)piperazin-1-yl]-4-benzylamino-6,7-dimethoxyquinazoline and 15 ml. of ethanol. Water (about 5 ml.)

was added to the cloud point, then 400 mg. of palladium-on-carbon (50% wet) catalyst. The resulting mixture was shaken in a Parr hydrogenation apparatus at 50 p.s.i. for 18 hours, filtered and the filtrate was slurried with 50 ml. of chloroform and filtered again. The filtrate was concentrated *in vacuo* to 10 ml., granulated for 15 minutes and filtered to obtain 450 mg. (56%) of the title compound, M.P. 263—265°C. identified by thin-layer chromatography on a silica gel plate (ethyl acetate/diethylamine 95:5 solvent system) and by comparison of the infrared spectrum with that obtained on an authentic sample of prazosin.

EXAMPLE 4

When the procedures of Examples 1 and 2 are repeated but employing the appropriately substituted benzylamine in each case in place of the benzylamine employed in Example 1, the following compounds are similarly obtained.



R_5	R_5
4—NO_2—	2—Br—
2—NO_2—	4—Br—
2—Cl—	2—CH_3—
3—Cl—	3—CH_3—
4—Cl—	4—CH_3—
3—CH_3O—	
4—CH_3O—	

EXAMPLE 5

When the procedure of Example 3 is repeated, but with any of the compounds obtained in Example 4 in place of 2-[4-(2-furoyl)piperazin-1-yl]-4-benzylamino-6,7-dimethoxyquinazoline, 2 - [4 - (2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline is obtained in like manner.

EXAMPLE 6

2-Chloro-4-phthalimido-6,7-dimethoxyquinazoline

To a 100 ml. three-necked, round bottomed flask fitted with thermometer, stirrer and drying tube was charged 50 ml. of N,N-dimethylformamide, 1.47 g. (0.010 mole) phthalimide and 0.48 g. (0.010 mole) of 50% w/w sodium hydride. After stirring at room temperature for thirty minutes a clear solution was obtained. To this was then added 2.59 g. (0.010 mole) of 2,4-dichloro-6,7-dimethoxyquinazoline and the resulting mixture was heated at 100°C. for 5 hours. The reaction mixture was cooled to room temperature, 150 ml. of water added and the precipitated product isolated by filtration and dried *in vacuo* to obtain 3.1 g. of the title compound, M.P. 255°C. The structure was verified by NMR and mass spectral data. Yield, 84%.

EXAMPLE 7

2-[4-(2-Furoyl)piperazin-1-yl]-4-phthalimido-6,7-dimethoxyquinazoline

To a 35 ml., one necked, round bottomed flask fitted with condenser and drying tube was placed 1.0 g. (0.0027 mole) 2-chloro-4-phthalimido-6,7-dimethoxyquinazoline, 10 ml. isoamyl alcohol and a solution of 0.550 g. (0.003 mole) 1-(2-furoyl)piperazine. The resulting mixture was heated at 130°C. for 4 hours, then cooled to room temperature. To the reaction mixture, 35 ml. of hexane was added and the precipitated product collected by filtration and dried to obtain 0.70 g. (47%) of the hydrochloride salt of the title compound. The purified free base was obtained from the salt by silica gel chromatography on a 2 inch×12 inch column, eluting with ethyl acetate/diethylamine (90:10). The purified product melted at 305°C.

When the above procedure is repeated but employing the indicated solvent in

place of isoamyl alcohol and the indicated temperature and reaction time, the title compound is likewise obtained.

Solvent	Reaction Temperature °C	Reaction Time, Hours
Isobutanol	50°	48
1,2-Dimethoxyethane	80°	30
Diethyleneglycol monoethyl ether	200°	1

EXAMPLE 8

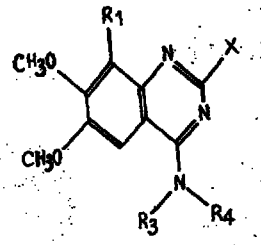
A solution of 95 milligrams (0.185 millimole) of 2-[4-(2-furoyl)piperazin-1-yl]-4-phthalimido-6,7-dimethoxyquinazoline in 2.0 ml. of concentrated hydrochloric acid was stirred at room temperature for two hours. Then 4.0 ml. of chloroform was added and the mixture adjusted to pH 10 by addition of sodium carbonate solution. The chloroform layer was separated and evaporated to dryness to obtain 55 mg. (77.6%) of 2 - [4 - (2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline, M.P. 270°C. The structure was verified by comparison of the infrared spectrum with that of an authentic sample, and by thin-layer chromatography on silica gel using a 95:5 ethyl acetate/diethylamine solvent system.

EXAMPLE 9

A suspension of 5.14 g. (0.01 mole) of 2-[4-(2-furoyl)piperazin-1-yl]-4-phthalimido-6,7-dimethoxyquinazoline in 200 ml. of isoamyl alcohol is heated to effect solution and 0.55 g. (0.011 mole) of hydrazine hydrate is added. The resulting solution is stored at 20°C. for 18 hours then evaporated to dryness under reduced pressure. The residue is triturated with 30 ml. of 0.5 N hydrochloric acid and stored at 4°C. for two hours. The solution was filtered to remove the precipitated phthalhydrazide. The filtrate is made alkaline (pH 10) with sodium hydroxide solution extracted with chloroform and the extracts concentrated to dryness to afford 2-[4-(2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline.

EXAMPLE 10

When the procedures of Example 1 and Example 6 are repeated but using the appropriate starting materials in each case the following compounds of formula (II) are obtained.

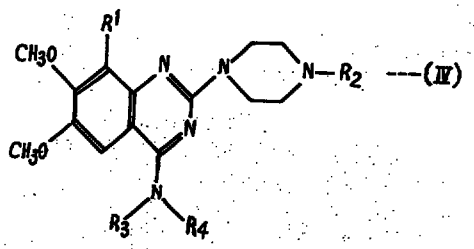


----(II)

X	R_1	R_3	R_4
Cl	H—	succinimido	
Br	H—	maleimido	
Cl	CH_3O—	phthalimido	
Br	CH_3O	succinimido	
Cl	CH_3O—	maleimido	
Br	H—	H	4—$CH_3OC_6H_4CH_2$—
Cl	CH_3O—	H	2—$BrC_6H_4CH_2$—
Cl	CH_3O—	H	$C_6H_5CH_2$
Cl	CH_3O—	H	4—$NO_2C_6H_4CH_2$—
Cl	H—	H	4—$ClC_6H_4CH_2$—
Br	CH_3O—	H	3—$CH_3C_6H_4CH_2$—
Br	H—	phthalimido	
Br	H—	H	$C_6H_5CH_2$—
Br	H—	H	4—$NO_2C_6H_4CH_2$—
Cl	CH_3O—	H	2—$NO_2C_6H_4CH_2$—
Br	H—	H	3—$ClC_6H_4CH_2$—

EXAMPLE 11

When the procedures of Examples 2 and 7 are repeated but in each case employing the appropriate compound of formula II selected from those provided in Example 10 and the appropriate 1-substituted piperazine as starting materials, the following compounds of formula (IV) are obtained.

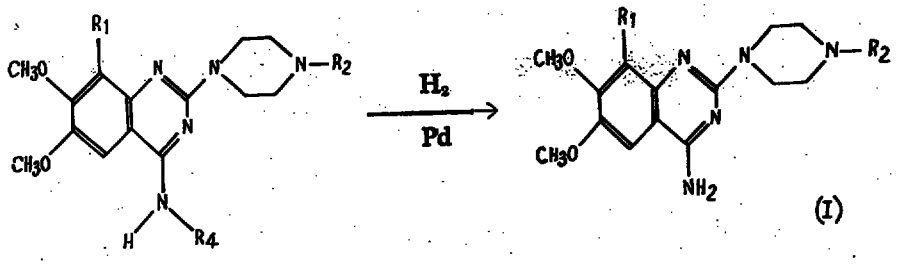


---(IV)

R_1	R_2	R_3	R_4
H—	$-CH_2CH=CH_2$	phthalimido	
H—	$-CH_2CH=CHCH_2CH_3$	succinimido	
CH_3O—	$-CH_2CH=C(CH_3)_2$	maleimido	
H—	$-COC_6H_5$	H	4—$CH_3OC_6H_5CH_2$—
CH_3O—	3-Furoyl	H	2—$BrC_6H_4CH_2$—
H—	3-thienylcarbonyl	phthalimido	
CH_3O—	2-thienylcarbonyl	H	4—$NO_2C_6H_4CH_2$—
H—	$-COOCH_3$	H	4—$ClC_6H_4CH_2$—
CH_3O—	$-COOCH_2CH_3$	H	3—$CH_3C_6H_4CH_2$—
CH_3O	$-COOCH_2CH(CH_3)_2$	phthalimido	
H—	$-COOCH_2CH(OH)CH_3$	H	$C_6H_5CH_2$—
CH_3O—	$-COOCH_2CHCH_3$ (CH$_3$)	H	$C_6H_5CH_2$—
CH_3O—	$-COOCH_2C(CH_3)_2$ (OH)	succinimido	
H	$-COOCH_2CHCH_3$ (OH)	H	4—$NO_2C_6H_4CH_2$—
CH_3O—	$-COOCH_2CHCH_2CH_3$ (OH)	maleimido	
H—	$-COC_6H_5$	phthalimido	
CH_3O—	2-thienylcarbonyl	phthalimido	
CH_3O—	3-thienylcarbonyl	H	2—$NO_2C_6H_4CH_2$—
H	$-CH_2CH=C(CH_3)_2$	H	3—$ClC_6H_4CH_2$—
CH_3O—	$-COOCH_2O=CH_2$ (CH$_3$)	phthalimido	
H	$-COOCH_2CH=CH_2$	succinimido	
H	$-COOCH_3$	maleimido	

EXAMPLE 12

Employing the catalytic hydrogenolysis procedure described in Example 3, but with the indicated starting material in each case selected from those provided in Example 11, the following compounds of formula (I) are obtained.

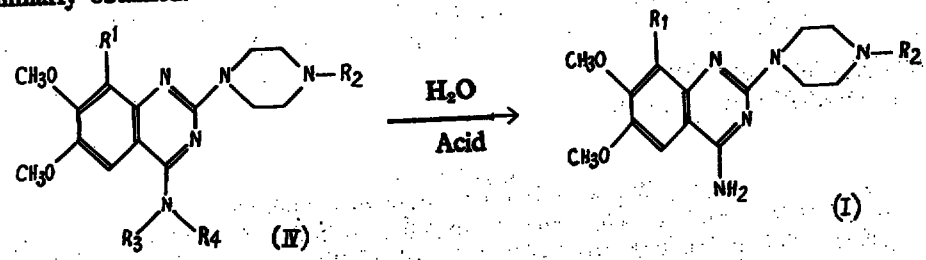


(I)

R_1	R_2	R_4
H—	$-COC_6H_5$	4—$CH_3OC_6H_4CH_2$—
CH_3O—	3-furoyl	2—$BrC_6H_4CH_2$—
CH_3O—	2-thienylcarbonyl	4—$NO_2C_6H_4CH_2$—
H—	$-COOCH_3$	4—$ClC_6H_4CH_2$—
CH_3O—	$-COOCH_2CH_3$	3—$CH_3C_6H_4CH_2$—
H—	$-COOCH_2CH(OH)CH_3$	$C_6H_5CH_2$—
CH_3O—	$-COOCH_2CHCH_3$ (CH$_3$)	$C_6H_5CH_2$—
H—	$-COOCH_2CHCH_3$ (OH)	4—$NO_2C_6H_4CH_2$—
CH_3O—	3-thienylcarbonyl	2—$NO_2C_6H_4CH_2$—
H—	$-CH_2CH=C(CH_3)_2$	3—$ClC_6H_4CH_2$—

EXAMPLE 13

When the appropriate compound of formula (IV), selected from those provided in Example 11, is hydrolyzed by the procedure of Example 8, but employing an equivalent amount of the indicated acid and carrying out the hydrolysis at the indicated temperature for the indicated time, the following compounds of formula (I) are similarly obtained.

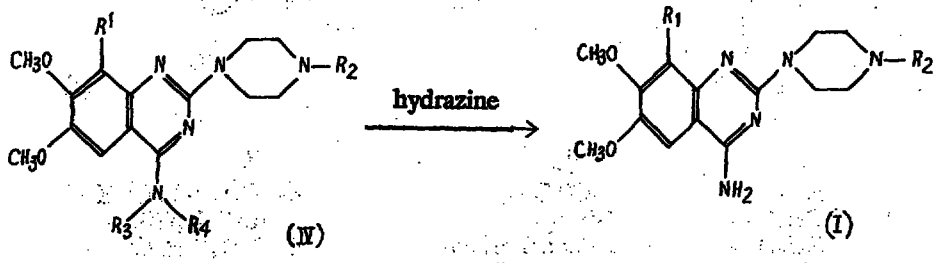


(IV) (I)

R_1	R_2	R_3+R_4	Acid	T°C	Time hours
H—	$-CH_2CH=CH_2$	phthalimido	48% hydrobromic	50°	1
H—	$-CH_2CH=CHCH_2CH_3$	succinimido	96% sulfuric	0°	6
CH_3O—	$-CH_2CH=C(CH_3)_2$	maleimido	85% phosphoric	100°	0.25
CH_3O—	$-COOCH_2CH(CH_3)_2$	phthalimido	37% hydrochloric	20°	2
CH_3O—	$-COOCH_2C(CH_3)_2$ (OH)	succinimido	48% hydrobromic	20°	3
CH_3O	$-COOCH_2CHCH_2CH_3$ (OH)	maleimido	37% hydrochloric	10°	4
H	$-COC_6H_5$	phthalimido	37% hydrochloric	20°	2
CH_3O—	2-thienylcarbonyl	phthalimido	37% hydrochloric	20°	2
H	3-thienylcarbonyl	phthalimido	37% hydrochloric	50°	0.75
CH_3O	$-COOCH_2-C(CH_3)=CH_2$	phthalimido	37% hydrochloric	25°	2
H	$-COOCH_3$	maleimido	80% sulfuric	25°	2

EXAMPLE 14

When the appropriate compound of formula (IV), selected from those provided in Example 11 is employed in place of 2-[4-(2-furoyl)piperazin-1-yl]-4-phthalimido-6,7-dimethoxyquinazoline in the procedure of Example 9 under the indicated conditions, the following final products of formula (I) are also obtained.



(IV) (I)

R_1	R_2	R_3+R_4	Solvent	T°C	Time hours
H—	$-CH_2CH=CHCH_2CH_3$	succinimido	isoamyl alcohol	100°	1
H—	$-COC_6H_5$	phthalimido	ethanol	50°	4
CH_3O—	2-thienylcarbonyl	phthalimido	n-butanol	0°	48
CH_3O—	$-COOCH_2CH(CH_3)_2$	phthalimido	DMF*	100°	0.5
CH_3O—	$-COOCH_2C(CH_3)_2$ | OH	succinimido	diglyme**	25°	20
CH_3O—	$-COOCH_2CHCH_2CH_3$ | OH	maleimido	ethanol	20°	24
CH_3O—	$-COOCH_2C=CH_2$ | CH_3	phthalimido	diglyme**	20°	18
H	3-thienylcarbonyl	phthalimido	isoamyl alcohol	50°	4
H	$-CH_2CH=CH_2$	phthalimido	ethanol	20°	18
H	$-COOCH_2CH=CH_2$	succinimido	DMF*	100°	1
H	$-COOCH_3$	maleimido	ethanol	0°	48

* N,N-Dimethylformamide
** Diethyleneglycol dimethylether

EXAMPLE 15

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

In a 100 ml. three-necked, round bottomed flask fitting with reflux condenser, thermometer and drying tube were placed 32 ml. of dry tetrahydrofuran, 10 ml. of dry N,N-dimethylformamide, 6.48 g. (0.025 mole) 2,4-dichloro-6,7-dimethoxyquinazoline [prepared by the procedure of Curd *et al.*, *J. Chem. Soc.*, 1759 (1948)], 3.03 g. (0.025 mole) of benzamide and 2.4 g. (0.050 mole) of 50% w/w sodium hydride, the hydride being added last. The resulting mixture was heated at reflux for 24 hours, cooled to room temperature and filtered, washing with tetrahydrofuran, to obtain 6.0 g. (66%) of the sodium salt of the title compound, M.P. 315°C.

Upon slurrying 1.0 g. of the sodium salt in 20 ml. of water, acidifying to pH 3—4 with 2N hydrochloric acid, stirring for 15 minutes at 20—25°C, filtering and drying overnight, 0.67 g. of the title compound was obtained. M.P. 235—240°C. Upon recrystallization from isoamyl alcohol, it melted at 236—238°C. The mass spectrum showed peaks at M/e 342 and 344.

EXAMPLE 16

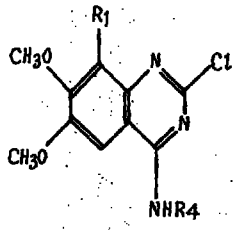
4-Acetylamino-2-chloro-6,7-dimethoxyquinazoline

In a 100 ml. reaction vessel were placed, 6.48 g. (0.025 mole) 2,4-dichloro-6,7-dimethoxyquinazoline, 1.5 g. (0.025 mole) acetamide, 32 ml. of dry N,N-dimethylformamide and 2.4 g. (0.050 mole) of 50% sodium hydride. Upon warming to 40°C., an exothermic reaction commenced and the temperature rapidly increased to 120°C. with considerable foaming. During this exothermic period the reaction mixture turned purple, then red. The mixture was cooled to 90°C. and maintained at this temperature

for two hours. The mixture was then cooled to room temperature, poured into 150 ml. of water, washed with two 100 ml. portions of chloroform and the aqueous phase adjusted to pH 2 by addition of concentrated hydrochloric acid. The precipitated product was collected by filtration and dried to obtain an 86% yield of the title compound, M.P. 275°C. Only one spot was obtained on thin-layer chromatography on silica gel, eluting with 95:5 ethyl acetate/diethylamine. The mass spectrum showed a molecular ion at M/e 281.

EXAMPLE 17

When the procedures of Examples 15 and 16 are repeated but with an equimolar amount of the appropriate alkylamide or arylamide in place of the amides employed therein, and in those cases where R_1 is methoxy, employing an equimolar amount of 2,4-dichloro-6,7,8-trimethoxyquinazoline, obtained by the procedure of U.S. 3,669,968, in place of 2,4-dichloro-6,7-dimethoxyquinazoline, the following compounds are prepared.



R_1	R_4	R_1	R_4
H—	HCO—	CH_3O—	HCO—
H—	CH_3CH_2CO—	CH_3O—	CH_3CO
H—	$CH_3CH_2CH_2CO$—	CH_3O—	$(CH_3)_2CHCO$—
H—	$(CH_3)_2CHCH_2CO$—	CH_3O—	$CH_3(CH_2)_2CO$
H—	4—ClC_6H_4CO—	CH_3O—	4—$CH_3C_6H_4CO$—
H—	2—BrC_6H_4CO	CH_3O—	4—$NO_2C_6H_4CO$—
H—	3—$NO_2C_6H_4CO$—	CH_3O—	3—ClC_6H_4CO—
H—	4—$CH_3OC_6H_4CO$—	CH_3O	C_6H_5CO—
H—	CF_3CO—	CH_3O	CF_3CO—

EXAMPLE 18

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

2,4-dichloro-6,7-dimethoxyquinazoline (6.48 g., 0.025 mole), 32 ml. tetrahydrofuran, ethylcarbamate (2.23 g., 0.025 mole) and 50% sodium hydride (2.4 g., 0.050 mole) was placed in a 100 ml. reaction flask fitted with thermometer reflux condenser and drying tube. The reaction mixture was refluxed for two hours after which 70 ml. of methanol was slowly added, the resulting mixture heated to 60°C. and filtered while hot. The filtrate was concentrated to a thick slurry, the solid collected by filtration washed with 5 ml. chloroform to obtain 5.4 g. (70%) of the title compound. A sample upon recrystallization from a mixture of tetrahydrofuran and hexane (2:3) melted at 212°C.

Anal. Calc'd for $C_{13}H_{14}N_3O_4Cl$ (percent): C, 50.09; H, 4.53; N, 13.48
Found: C, 49.95; H, 4.46; N, 13.54

EXAMPLE 19

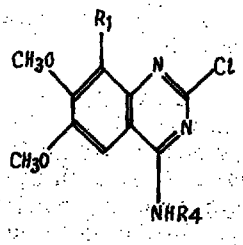
4-Phenoxycarbonylamino-2-chloro-6,7,8-trimethoxyquinazoline

In a 500 ml. flask is placed 25.4 g. (0.10 mole) 2,4-dichloro-6,7,8-trimethoxyquinazoline prepared as described in U.S. 3,669,968, 13.7 g. (0.10 mole) phenylcarbamate (Aldrich Chemical Co.), 130 ml. tetrahydrofuran and 9.6 g. (0.20 mole) of a 50% dispersion of sodium hydride. The resulting mixture is refluxed for 4 hours, cooled to room temperature, 250 ml. of methanol is added and the mixture warmed to 60°C. and filtered. The filtrate is concentrated to a thick slurry, the solid collected by filtration and washed with chloroform to obtain the title compound.

When 2,4-dibromo-6,7,8-trimethoxyquinazoline is employed in the above procedure in place of 2,4-dichloro-6,7,8-dimethoxyquinazoline, 4-phenoxycarbonylamino-2-bromo-6,7,8-trimethoxyquinazoline is similarly obtained.

EXAMPLE 20

When the procedures of Examples 18 and 19 are repeated, but employing the appropriate starting materials in each case, the following compounds are likewise obtained.



R_1	R_4	R_1	R_4
H	CH_3OCO—	CH_3O—	CH_3CH_2OCO—
H	$(CH_3)_3COCO$—	CH_3O—	$(CH_3)_2CHOCO$—
H	C_6H_5OCO—	CH_3O—	$CH_3(CH_2)_3OCO$—
H	4—ClC_6H_4OCO—	CH_3O—	4—BrC_6H_4OCO—
H	2—BrC_6H_4OCO—	CH_3O—	3—$CH_3C_6H_4OCO$—
H	3—$CH_3OC_6H_4OCO$—	CH_3O—	4—$NO_2C_6H_4OCO$—
H	4—$NO_2C_6H_4OCO$—	CH_3O—	$C_6H_5CH_2OCO$—
H	4—$ClC_6H_4CH_2OCO$—	CH_3O—	4—$BrC_6H_4CH_2OCO$—
H	2—$CH_3C_6H_4CH_2OCO$—	CH_3O—	2—$CH_3OC_6H_4CH_2OCO$—
H	2—$NO_2C_6H_4CH_2OCO$—	CH_3O—	4—$ClC_6H_4CH_2OCO$—

EXAMPLE 21

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

To a 50 ml. flask fitted with stirrer, reflux condenser and drying tube was added 160 mg. (0.66 mmole) 4-benzoylamino-2-chloro-6,7-dimethoxyquinazoline prepared by the procedure of Examples 15, 244.2 mg. (1.32 mmole) 1-(2-furoyl)piperazine and 4 ml. of isoamyl alcohol. The resulting mixture was heated at 100°C. for 4 hours then cooled to room temperature. The precipitated solid was collected by filtration and dried, to obtain 60 mg. of crude product. It was identified as 2-[4-(2-furoyl)-piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline by silica gel thin-layer chromatography (ethylacetate/diethylamine 90:10). The crude material was purified on a 0.5 inch×9 inch column of silica gel, eluting with benzene/acetone/formic acid/water (100:100:20:5, by volume) to provide 35 mg., M.P. 275°C.

When the above procedure is repeated but employing the indicated solvent in place of isoamyl alcohol and carrying out the reaction employing the tabulated temperature and time in each case, the title compound is obtained in like manner.

Solvent	Reaction Temperature, °C.	Reaction Time, Hours
2-Butanol	50°	50
2-Methoxyethanol	80°	18
2-Methyl-2-pentanol	130°	2
Diethyleneglycol	200°	0.25

EXAMPLE 22

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

4-Ethoxycarbonylamino-2-chloro-6,7-dimethoxyquinazoline, (2.0 g., 0.0064 mole) and 23 ml. of isoamyl alcohol were combined in a reaction flask. A solution of 1-(2-furoyl)piperazine (2.54 g., 0.014 mole) in 18 ml. of isoamyl alcohol was added and the mixture heated at 130°C. for 4 hours. The precipitated solids were collected on a filter funnel, washed with isoamyl alcohol then stirred with 100 ml. of 10% aqueous sodium hydroxide. An equal volume of chloroform was added and the mixture stirred for 15 minutes. The organic layer was separated, concentrated to about 25 ml. and 50 ml. of tetrahydrofuran added. The solids were collected by filtration then further purified by chromatography on a silica gel column (1×18 inches) eluting first with ethylacetate, then with methanol. The fractions containing the title compound were combined and evaporated to dryness. The residue was taken up in 10 ml. of chloroform, hexane added to the cloud point, stirred 15 minutes and the crystals collected by filtration, M.P. 265°C., yield 900 mg. (37%).

When the above reaction is repeated at 80°C. for 18 hours, the results are substantially unchanged.

EXAMPLE 23

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

4-Acetylamino-2-chloro-6,7-dimethoxyquinazoline (28.2 g., 0.10 mole), 1-benzoylpiperazine (38.0 g., 0.20 mole) and 750 ml. of isoamyl alcohol are combined. The resulting mixture is refluxed for three hours then cooled to room temperature. The precipitated product was filtered, washed with ethylacetate, then with ether and air dried to obtain the title compound.

EXAMPLE 24

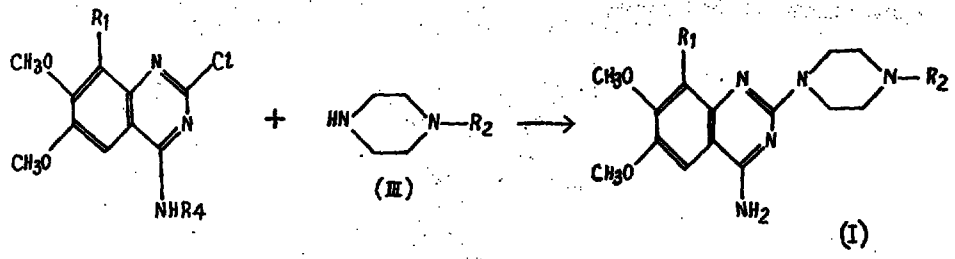
2-[4-(2-Hydroxy-2-methylprop-1-yloxycarbonyl)piperazin-1-yl]-4-amino-6,7,8-trimethoxyquinazoline

4-Phenoxycarbonylamino-2-chloro-6,7,8-trimethoxyquinazoline (19.5 g., 0.05 mole), 1-(2-hydroxy-2-methylprop-1-yloxycarbonyl)piperazine (20.2 g., 0.10 mole) and 500 ml. of diethyleneglycol dimethylether are heated at 125°C. for two hours. The reaction mixture is concentrated *in vacuo* to about 200 ml. and an equal volume of ethyl ether is added. The precipitated hydrochloride salt is filtered, washed with ether then stirred with 200 ml. of saturated aqueous sodium carbonate solution. The liberated base is extracted with 3×200 ml. portions of chloroform and the extracts concentrated to about 150 ml. Diisopropyl ether, about 100 ml., is added and the mixture set aside overnight, then filtered to yield the crystalline title compound.

When the above procedure is repeated with an equimolar amount of 4-phenoxycarbonylamino-2-bromo-6,7,8-trimethoxyquinazoline in place of the corresponding 2-chloro compound and the reaction mixture is maintained at 50°C. for 40 hours, at 80°C. for 15 hours, or at 200°C. in a high pressure reactor for 25 minutes the title compound is obtained in the same manner.

EXAMPLE 25

When the compounds obtained in Examples 17 and 20 are reacted with the appropriately substituted piperazines of formula (III) by the procedures of Examples 21 through 24, the following compounds of formula (I) are similarly obtained.

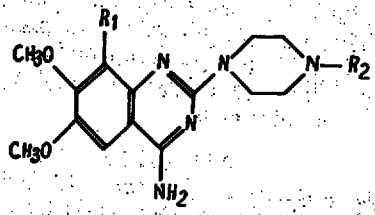


R_1	R_4	R_2
H—	HCO—	—$CH_2CH{=}CH_2$
H—	CH_3CH_2CO—	—$CH_2C(CH_3){=}CH_2$
H—	$CH_3CH_2CH_2CO$—	—$CH_2C(CH_3){=}CHCH_3$
H—	$(CH_3)_2CHCH_2CO$—	—COC_6H_5
H—	4—ClC_6H_4CO—	2-furoyl
H—	2—BrC_6H_4CO—	3-furoyl
H—	3—$NO_2C_6H_4CO$—	2-thienylcarbonyl
H—	4—$CH_3OC_6H_4CO$—	3-thienylcarbonyl
CH_3O—	HCO—	—$COOCH_3$
CH_3O—	CH_3CO—	—$COOCH_2CH_3$
CH_3O—	$(CH_3)_2CHCO$—	—$COOCH_2(CH_2)_2CH_3$
CH_3O—	$CH_3(CH_2)_2CO$—	—$COOCH_2CH{=}CH_2$
CH_3O—	4—$CH_3C_6H_4CO$—	—$COOCH_2C(CH_3){=}CH_2$
CH_3O—	4—$NO_2C_6H_4CO$—	—$COOCH_2CH{=}CHCH_3$
CH_3O—	3—ClC_6H_4CO—	—$COOCH_2C(OH)(CH_3)_2$
CH_3O—	C_6H_5CO—	—$COOCH_2CH(OH)CH_3$
H—	CH_3OCO—	—$COOCH_2CH(OH)CH_3$
H—	CF_3CO—	2-furoyl
H—	$(CH_3)_2COCO$—	—$COOCH_2C(OH)(CH_3)_2$
H—	C_6H_5OCO—	—$COOCH_2C(CH_3){=}CH_2$

R_1	R_4	R_2
H—	4—ClC_6H_4OCO—	—$COOCH_2CH{=}CH_2$
H—	2—BrC_6H_4OCO—	—$COOCH_2CH(CH_3)_2$
H—	4—$NO_2C_6H_4OCO$—	—$COOCH(CH_3)_2$
H—	4—$ClC_6H_4CH_2OCO$—	—$COOCH_3$
H—	2—$CH_3C_6H_4CH_2OCO$—	2-thienylcarbonyl
H—	2—$NO_2C_6H_4CH_2OCO$—	2-furoyl
CH_3O—	CH_3CH_2OCO—	3-furoyl
CH_3O—	$(CH_3)_2CHOCO$—	2-furoyl
CH_3O—	$CH_3(CH_2)_3OCO$—	—$CH_2CH{=}CH_2$
CH_3O—	4—BrC_6H_4OCO—	—$CH_2C(CH_3){=}CH_2$
CH_3O—	3—$CH_3C_6H_4OCO$—	—$CH_2C(CH_3){=}CH_2$
CH_3O—	4—$NO_2C_6H_4OCO$—	—COC_6H_5
CH_3O—	$C_6H_5CH_2OCO$—	—$COOCH_2CH{=}CH_2$
CH_3O—	4—$BrC_6H_4CH_2OCO$—	—$COOCH_2C(CH_3){=}CH_2$
CH_3O—	2—$CH_3OC_6H_4CH_2OCO$—	—$COOCH_3$
CH_3O—	4—$ClC_6H_4CH_2OCO$—	—$COOCH_2CH_3$
CH_3O—	CF_3CO	—$COOCH_2C(CH_3){=}CH_2$

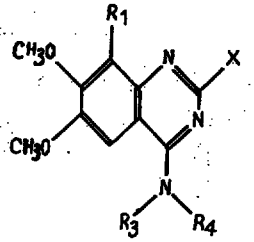
WHAT WE CLAIM IS:—

1. A process for preparing a final product of the formula



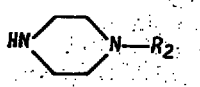
----(I)

or a hydrochloride or hydrobromide salt thereof, which comprises reacting one mole of a first reactant of the formula



----(II)

with from one to two moles of a second reactant of the formula



---(III)

in a reaction inert organic solvent at a temperature from 50° to 200°C. and, if necessary, thereafter removing the amino-protecting group;

wherein X is Cl or Br;

R_1 is hydrogen or methoxy;

R_2 is alkenyl having from three to five carbon atoms, benzoyl; furoyl, thienylcarbonyl, alkoxycarbonyl having from two to five carbon atoms, alkenyloxycarbonyl having from four to five carbon atoms or (2-hydroxyalkoxy)carbonyl having from four to five carbon atoms;

when taken separately, R_3 is hydrogen and R_4 is $—CH_2C_6H_4R_6$,

$—COCH_2C_6H_4R_6$, $—CR_6$, $—CCF_3$, $—CH$ or $—COR_6$,

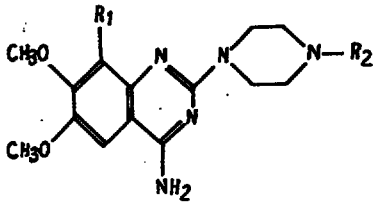
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or when R_3 and R_4 are taken together with the nitrogen atom to which they are attached, they form a phthalimido, maleimido or succinimido group,

R_1	R_4	R_2
H—	4—ClC_6H_4OCO—	—$COOCH_2CH{=}CH_2$
H—	2—BrC_6H_4OCO—	—$COOCH_2CH(CH_3)_2$
H—	4—$NO_2C_6H_4OCO$—	—$COOCH(CH_3)_2$
H—	4—$ClC_6H_4CH_2OCO$—	—$COOCH_3$
H—	2—$CH_3C_6H_4CH_2OCO$—	2-thienylcarbonyl
H—	2—$NO_2C_6H_4CH_2OCO$—	2-furoyl
CH_3O—	CH_3CH_2OCO—	3-furoyl
CH_3O—	$(CH_3)_2CHOCO$—	2-furoyl
CH_3O—	$CH_3(CH_2)_3OCO$—	—$CH_2CH{=}CH_2$
CH_3O—	4—BrC_6H_4OCO—	—$CH_2C(CH_3){=}CH_2$
CH_3O—	3—$CH_3C_6H_4OCO$—	—$CH_2C(CH_3){=}CH_2$
CH_3O—	4—$NO_2C_6H_4OCO$—	—COC_6H_5
CH_3O—	$C_6H_5CH_2OCO$—	—$COOCH_2CH{=}CH_2$
CH_3O—	4—$BrC_6H_4CH_2OCO$—	—$COOCH_2C(CH_3){=}CH_2$
CH_3O—	2—$CH_3OC_6H_4CH_2OCO$—	—$COOCH_3$
CH_3O—	4—$ClC_6H_4CH_2OCO$—	—$COOCH_2CH_3$
CH_3O—	CF_3CO	—$COOCH_2C(CH_3){=}CH_2$

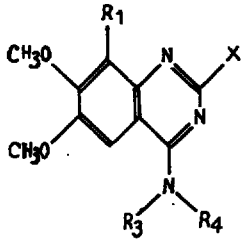
WHAT WE CLAIM IS:—

1. A process for preparing a final product of the formula



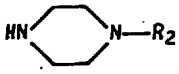
----(I)

or a hydrochloride or hydrobromide salt thereof, which comprises reacting one mole of a first reactant of the formula



----(II)

with from one to two moles of a second reactant of the formula



---(III)

in a reaction inert organic solvent at a temperature from 50° to 200°C. and, if necessary, thereafter removing the amino-protecting group;

wherein X is Cl or Br;

R_1 is hydrogen or methoxy;

R_2 is alkenyl having from three to five carbon atoms, benzoyl, furoyl, thienylcarbonyl, alkoxycarbonyl having from two to five carbon atoms, alkenyloxycarbonyl having from four to five carbon atoms or (2-hydroxyalkoxy)carbonyl having from four to five carbon atoms;

when taken separately, R_3 is hydrogen and R_4 is $—CH_2C_6H_4R_5$,

$—\overset{\overset{O}{\|}}{C}OCH_2C_6H_4R_5$, $—\overset{\overset{O}{\|}}{C}R_5$, $—\overset{\overset{O}{\|}}{C}CF_3$, $—\overset{\overset{O}{\|}}{C}H$ or $—\overset{\overset{O}{\|}}{C}OR_5$,

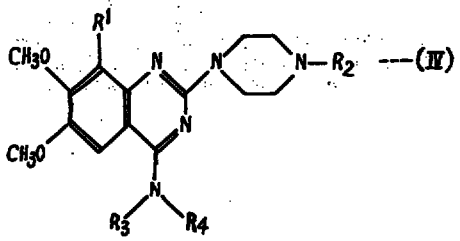
or when R_3 and R_4 are taken together with the nitrogen atom to which they are attached, they form a phthalimido, maleimido or succinimido group,

R_5 is hydrogen, chloro, bromo, methyl, methoxy or nitro;

R_6 is an alkyl group having from one to four carbon atoms or $-C_6H_4R_5$.

2. The process according to claim 1 wherein said reaction is carried out at a temperature from 80° to 130°C.

3. The process according to claim 1 wherein when R_2 is benzoyl, furoyl, thienylcarbonyl, alkoxycarbonyl having from two to five carbon atoms or (2 hydroxyalkoxy)-carbonyl having from four to five carbon atoms; R_3 is hydrogen and R_4 is $-CH_2C_6H_4R_5$, equimolar amounts of said reactants are reacted to form an intermediate of the formula

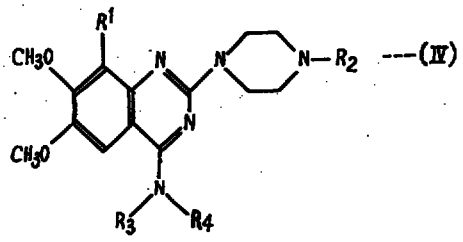


---(III)

or a hydrochloride or hydrobromide salt thereof, and said intermediate is further reacted by catalytic hydrogenolysis to form said final product.

4. The process according to claim 3 wherein said catalytic hydrogenolysis a palladium catalyst is employed.

5. The process according to claim 1 wherein when R_3 and R_4 taken together with the nitrogen atom to which they are attached form a phthalimido, maleimido or succinimido group, equimolar amounts of said reactants are reacted to form an intermediate of the formula



---(IV)

or a hydrochloride or hydrobromide salt thereof, and said intermediate is further reacted at a temperature from 0° to 100°C. to form said final product by

a. hydrolysis, or

b. reaction with an equimolar amount of hydrazine in the presence of a reaction inert organic solvent.

6. The process according to claim 5 wherein said hydrolysis is carried out using hydrochloric, hydrobromic, sulfuric or phosphoric acid.

7. The process according to claim 5 wherein said intermediate is further reacted at a temperature from 20° to 50°C.

8. The process according to claim 1 wherein when R_3 is hydrogen and R_4 is

$$-COCH_2C_6H_4R_5, \quad -\overset{\overset{O}{\|}}{C}R_6, \quad -\overset{\overset{O}{\|}}{C}CF_3, \quad -\overset{\overset{O}{\|}}{C}H \quad \text{or} \quad \overset{\overset{O}{\|}}{C}OR_6$$

where R_5 and R_6 are as defined in claim 1, one mole of said first reactant and two moles of said second reactant are reacted to directly provide said final product.

9. The process according to claim 1 wherein R_1 is hydrogen and R_2 is 2-furoyl.

10. The process according to claim 1 wherein R_1 is methoxy and R_2 is 2-methyl-2-hydroxyprop-1-yloxycarbonyl.

11. The process according to claim 1 wherein R_1 is methoxy and R_2 is 2-methylprop-2-enyloxycarbonyl.

12. The process according to claim 1 wherein X is Cl.

13. A process as claimed in claim 1 and substantially as hereinbefore described in any one of the Examples 2—5, 7—9, 12—14 and 21—25.

14. 2-(4-Substituted piperazin-1-yl)-4-aminoquinazolines of the formula I as defined in claim 1 when made by the process of any one of claims 1 to 12 and 16.

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