1 464 583

PATENT SPECIFICATION

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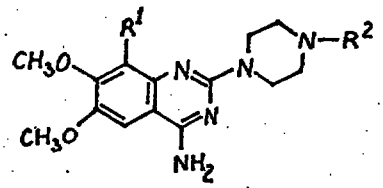
(54) PREPARATION OF QUINAZOLINE DERIVATIVES

(71) We, PFIZER INC., a corporation organized under the laws of the State of Delaware, United States of America, of 235 East 42nd Street, 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: —

This invention relates to a process for the preparation of quinazoline derivatives valuable as hypotensive agents by virtue of their ability to lower blood pressure in hypertensive mammals. More specifically, these hypotensive agents are 6,7-dimethoxy-4-amino-2-(4-substituted piperazin-1-yl) quinazolines and 6,7,8-trimethoxy-4-amino-2-(4-substituted piperazin-1-yl) quinazolines, use of which is disclosed in United States Patent Specifications No. 3,511,836 and 3,669,968.

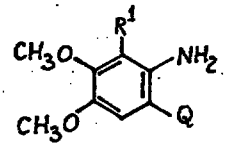
United States Patent Specification No. 3,511,836 discloses several processes for the preparation of 6,7-dimethoxy-4-amino-2-(4-substituted piperazin-1-yl)-quinazolines. For example, according to the said Specification they may be prepared by reaction of 6,7 - dimethoxy - 4 - amino - 2 - chloroquinazoline with an appropriate 1 - monosubstituted piperazine, or, alternatively, by reaction of either 4,5 - dimethoxy - 2 - aminobenzonitrile or 4,5 - dimethoxy - 2 - aminobenzamidine with an appropriate 1 - amidino - 4 - substituted piperazine. United States Patent Specification No. 3,669,968 discloses the preparation of 6,7,8 - trimethoxy - 4 - amino - 2 - (4 - substituted piperazin - 1 - yl)quinazolines *via* the reaction of 6,7,8 - trimethoxy - 4 - amino - 2 - chloroquinazoline with an appropriate 1 - monosubstituted piperazine. In Netherlands Patent Specification No. 7206067, there is disclosed a process which comprises reacting certain *o* - aminobenzonitriles with cyanamides to produce 2,4 - diaminoquinazoline derivatives.

In accordance with the present invention there is provided a process for the preparation of a quinazoline derivative having the general formula: —



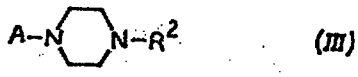
(I)

which comprises reacting a compound having the general formula: —



(II)

or a salt thereof, with a compound having the general formula: —



(III)

or a salt thereof, in a reaction-inert, organic solvent, wherein R^1 is a hydrogen atom or a methoxy group R^2 an alkenyl group containing three, four or five carbon atoms, a benzoyl, furoyl or thienylcarbonyl group, an alkoxycarbonyl group containing from two to five carbon atoms, an alkenyloxycarbonyl group containing four or five carbon atoms or a (2 - hydroxyalkoxy) carbonyl group containing four or five carbon atoms Q is a cyano group or a group of the formula —C=(NH)—NH_2 and A is a cyano group or a group of the formula —C=(NH)—X—R^3, wherein X is an oxygen or sulphur atom and R^3 is an alkyl group containing one to six carbon atoms provided that when Q is a cyano group A is —C(=NH)—X—R^3.

A particularly desirable embodiment of the process of the present invention as regards the availability of starting materials and ease of operation, is the embodiment wherein Q is a cyano group and A is —C(=NH)—X—R^3. Preferred examples of R^3 are alkyl groups which correspond to the alkyl group of readily available alkanols, such as, for example, methanol, ethanol and isopropanol. Whereas the present 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 compounds: namely, 6,7 - dimethoxy - 4 - amino - 2 - [4 - (2 - furoyl)piperazine - 1 - yl] quinazoline and 6,7,8 - trimethoxy - 4 - amino - 2 - [4 - (2 - hydroxy - 2 - methylprop - 1 - yloxycarbonyl)piperazin -1- yl] quinazoline, known in the art as prazosin and trimazosin, respectively. 6,7,8 - Trimethoxy - 4 - amino - 2 - [2 - methylprop - 2 - enyloxycarbonyl) piperazin - 1 - yl]quinaxoline is a valuable starting material for the preparation of trimazosin (United States Patent Specification No. 3,669,968). Prazosin and trimaxosin have recently been reported to have therapeutic utility in man (Cohen, *Journal* of *Clinical Pharmacology, 10,* 408, [1970]; de duia, et al., *Current Therapeutic Research,* 15, 339, (1973).

The process of the present invention is carried out by reacting, preferably by heating, together the starting reagents in an appropriate, reaction-inert, organic solvent, optionally in the presence of a basic catalyst. An appropriate solvent is one which will serve to dissolve at least one of the reactants, and will not adversely interact with either the starting reagents, or the product. Examples of such solvents are alkanols, such as methanol, ethanol, isopropanol and butanol; ethers, such as diethylether, tetrahydrofuran, dioxan and 1,2 - dimethoxyethane; aromatic hydrocarbons, such as benzene, toluene and xylene; tertiary amides such as *N,N* - dimethylformamide, *N,N* - dimethylacetamide and N - methylpyrrolidone; dimethylsulphoxide; and pyridine. The reaction may be carried out over a wide range of temperatures, but a temperature within the range of 50°C. to 180°C. is preferably used, and a particularly convenient temperature range is from 80°C. to 130°C. The reaction time needed for the present process varies according to several factors, such as, for example, the reaction temperature, the reactivity of the starting reagents and the concentrations of the reactants. At a lower temperature a longer reaction period is needed while at a higher temperature the reaction is completed in a shorter time. In any even, reaction times of several hours, for example, from two hours to twenty-four hours, are commonly used.

Although the starting reagents are preferably contacted in equimolar proportions, this is not essential to the success of the reaction, and an excess of either reagent may be present.

The quinazoline derivative of formula (I) produced by the present process is recovered from the reaction medium by methods well known in the art. For example, if the product precipitates during the course of the reaction, it may be recovered simply by filtration. Alternatively, when the product does not precipitate spontaneously, it often may be induced to precipitate at the end of the reaction by dilution of the reaction medium with a non-solvent, such as hexane or water. A further method of product recovery involves removal of the solvent by evaporation, followed by partitioning of the crude product thus obtained between water and a water-immiscible organic solvent. After separation of the two phases, the product-containing phase is evaporated, to yield the product.

The compounds of formula (III), wherein A is —C(=NH)—X—R^3, have basic properties, and they will form acid-addition salts. For example, they will form acid-addition salts with such acids as hydrohalic acids, for example, hydrogen chloride and hydrogen bromide, sulphonic acids, for example, methanesulphonic acid, benzenesulphonic acid and *p*-toluenesulphonic acid, and certain alkanoic acids, for example,

trifluoroacetic acid and trichloroacetic acid. Moreover, the acid-addition salts of the compounds of formulae (II) and (III) may serve successfully as starting reagents in the process for the production of the quinazoline compounds of formula (I). Thus, in the reaction of a compound of formula (II) with a compound of formula (III), either or both of the starting reagents may be used in the form of its free base, or its acid-addition salt, and this successfully leads to the formation of the corresponding compound of formula (I).

However, from a standpoint of speeding up the rate of reaction between a compound of formula (II) and a compound of formula (III) and also of obtaining a good yield of product, it is desirable to carry out the reaction in the presence of a basic catalyst. In this case, it is usual to carry out the reaction in the presence of a net excess of from 0.5 molar equivalents to five molar equivalents of a basic catalyst, and preferably in the presence of a net excess of one molar equivalent of a basic catalyst. However, even larger amounts of catalyst, for example, up to about ten molar equivalents, are sometimes used. The figure for the net excess of basic catalyst is based on which ever reagent II or III is in the smaller amount. If one of the starting reagents is used in the form of its acid-addition salt, one molar equivalent of added basic catalyst is consumed in neutralizing the said acid-addition salt. Consequently in this case, it is necessary to add to the reaction medium at least two molar equivalents of basic catalyst in order to have one molar equivalent of basic agent available to catalyze the reaction. Analogously, when both of the starting reagents are used in the form of their acid-addition salts, it is desirable to add to the reaction medium at least three molar equivalents of basic catalyst.

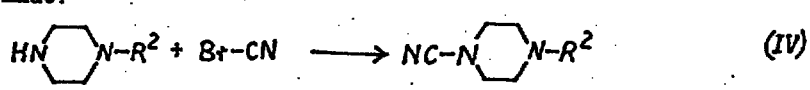
A wide variety of basic catalysts may be used in the present process, such as organic tertiary amines, for example, triethylamine, tributylamine, *N,N* - dimethylaniline, *N* - methylmorpholine, pyridine and quinoline; metal hydrides, for example, sodium hydride, potassium hydride and calcium hydride; metal alkoxides, such as sodium methoxide, potassium methoxide and sodium ethoxide; metal alkyls, for example, methyllithium; metal pheryls, for example, phenyllithium; and metal salts of amines, for example, lithium isopropylamide.

It will be realized that not all the conditions given above are equally effective or convenient in all cases for the reaction of a compound of formula (II) with a compound of formula (III). Thus the skilled artist will make a selection of appropriate reaction conditions in each case, based on such factors as the stability and reactivity of the starting reagents and the product, the scale of the reaction contemplated, the availability of starting reagents and the ease of isolating the particular product. In particular, the skilled artist will ensure the compatibility of the solvent and basic catalyst chosen, and also ensure that starting reagents and products are not exposed to conditions which would lead to their decomposition.

A variation which is used in some instances for the process of the present invention comprises the steps of: (1) contacting the starting reagents, or acid-addition salts thereof, in a solvent such as those delineated hereinbefore, for a few hours; and then (2) adding to the on-going reaction an appropriate quantity of a basic catalyst, to complete the conversion to quinazoline.

The starting reagent of formula (II), wherein R^1 is a hydrogen atom and Q is a cyano group namely, 2 - amino - 4,5 - dimethoxybenzonitrile, is prepared from 3,4 - dimethoxybenzonitrile by nitration followed by reduction with stannous chloride, as taught by McKee, McKee and Bost, *Journal of the American Chemical Society, 68*, 1902 (1946), and references cited therein. The starting reagent of formula (II) wherein R^1 is a methoxy group and Q is a cyano group namely, 2 - amino - 3,4,5 - trimethoxy - benzonitrile, is prepared in analogous fashion from 3,4,5 - trimethoxybenzonitrile, by nitration followed by stannous chloride reduction. Preparation of the starting reagents of formula (II), wherein Q is —C(==NH)—NH_2, namely 4,5 - dimethoxy - 2 - aminobenzamidine and 3,4,5 - trimethoxy - 2 - aminobenzamidine, is achieved by treating the corresponding compound of formula (II), wherein Q is a cyano group with hydroxylamine, followed by catalytic hydrogenation, using the method and conditions described by Carrington (*Journal of the Chemical Society*, London 2527 [1955]) for the conversion of anthranilonitrile into 2 - aminobenzamidine.

The starting reagents of formula (III), wherein A is a cyano group may be prepared by reaction of the appropriate 1 - monosubstituted piperazine (IV) with cyanogen bromide:



(IV)

The reaction may be carried out by contacting equimolar amounts of the piperazine and cyanogen bromide, according to the method described in Netherlands Patent Specification No. 7206067 for the reaction of cyanogen bromide with 1-(2-furoyl) piperazine.

The starting reagents of formula (III), wherein A is —C(=NH)—O—R^3, are prepared from the corresponding compound of formula (III), wherein A is a cyano group by reaction with an alkanol of formula R^3OH, in the presence of an acid catalyst. The reaction is usually carried out by dissolving equimolar amounts of the starting cyano compound and alkanol in an appropriate aprotic solvent, such as, for example, diethyl ether, tetrahydrofuran, chloroform or methylene chloride, and then saturating the solution with hydrogen chloride at 0°C. The reaction mixture is then stored at a temperature from 0°C. to ambient temperature, for a few hours, for example overnight, and then the product is recovered. In some instances the hydrochloride salt of the product precipitates, in which case it is simply filtered off. When the product does not precipitate, the solvent is removed by evaporation, leaving the hydrochloride salt of the product. The hydrochloride salt may be converted into a free base by conventional means. Other techniques known in the art for the conversion of cyano compounds into imino esters, also may be used for the preparation of the compounds of formula (III) wherein A is —C(=NH)—O—R^3 (e.g., *Shriner* and *Neuman, Chemical Reviews, 35,* 354—358 [1944]).

Preparation of the starting reagents of formula (III) wherein A is —C(=NH)—S—R^3 may be achieved using the method described above for the preparation of the corresponding compounds of formula (III) wherein A is —C(=NH)—O—R^3, by replacing the alkanol used therein by an appropriate alkyl mercaptan of formula R^3SH. Alternatively, the compounds of formula (III) wherein A is —C(=NH)—S—R^3 may be prepared from the appropriate 1 - monosubstituted piperazine of formula (IV), by a two-step procedure which comprises: (1) reaction of the said piperazine derivative with ammonium thiocyanate, and (2) alkylation of the thiocarbonoyl piperazine thus formed with an alkyl halide or alkyl sulphonate of formula R^3Y, wherein Y is a chlorine, bromine or iodine atom or a methanesulphonyloxy, benzenesulphonyloxy or *p* - toluenesulphonyloxy group. The two steps are each carried out in conventional fashion. Techniques for the reaction of amines with ammonium thiocyanate, and for the alkylation of thioureas, are discussed in Houben-Weyl's "Methoden der Organischen Chemie", Volume 9, 1955, pp 887—889 and 900—903.

The following Examples illustrate the present invention, and the manner in which it may be performed.

EXAMPLE I

[Q is CN; A is —C(=NH)—O—C_2H_5]

To a stirred solution of 1.78 g. (0.01 mole) of 4,5 - dimethoxy - 2 - aminobenzonitrile in 30 ml. of *N,N* - dimethylformamide is added 2.88 g. (0.01 mole) of ethyl 4 - (2 - furoyl) piperazin - 1 - ylformimidate hydrochloride, followed by 855 mg. (0.02 mole) of a 56.1% dispersion of sodium hydride in mineral oil. The reaction mixture is stirred at ambient temperature for 30 minutes, and then it is heated to *ca.* 100°C. and maintained at that temperature for 12 hours. The reaction mixture is cooled to ambient temperature, diluted with an excess of water, and then extracted with chloroform. The chloroform extract is washed several times with water, dried using anhydrous magnesium sulphate, and then evaporated to dryness *in vacuo*. This affords crude 6,7 - dimethoxy - 4 - amino - 2 - [4 - (2 - furoyl)piperazin - 1 - yl] quinazoline, which is purified further by recrystallization from aqueous ethanol.

EXAMPLE II

When the procedure of Example I is repeated, and the ethyl 4 - (2 - furoyl) piperazin - 1 - ylformimidate hydrochloride used therein is replaced by an equimolar amount of:

Methyl 4 - (2 - furoyl)piperazin - 1 - ylformimidate hydrochloride,
n - propyl 4 - (2 - furoyl)piperazin - 1 - ylformimidate hydrochloride
isobutyl 4 - (2 - furoyl)piperazin - 1 - ylformimidate hydrochloride
isopentyl 4 - (2 - furoyl)piperazin - 1 - ylformimidate hydrochloride
n - hexyl 4 - (2 - furoyl)piperazin - 1 - ylformimidate hydrochloride

methyl 4 - (2 - furoyl)piperazin - 1 - ylthioformimidate hydroiodide
ethyl 4 - (2 - furoyl)piperazin - 1 - ylthioformimidate hydrobromide and
isopropyl 4 - (2 - furyl)piperazin - 1 - ylthioformamidate hydrobromide,

respectively, the product in each case is 6,7 - dimethoxy - 4 - amino - 2 - (4 - [2 - furoyl]piperazin - 1 - yl)quinazoline.

EXAMPLE III

The procedure of Example I is repeated, except that the ethyl 4 - (2 - furoyl)-piperazin - 1 - ylformimidate hydrochloride used therein is replaced by an equimolar amount of:

ethyl 4 - allylpiperazin - 1 - ylformimidate methane-sulfonate
Methyl 4 - benzoylpiperazin - 1 - ylformimidate hydrochloride
isopropyl 4 - (3 - furoyl) piperazin - 1 - ylformimidate hydrochloride
methyl 4 - (allyloxycarbonyl)piperazin - 1 - ylthioformimidate hydroiodide
ethyl 4 - (2 - methylprop - 2 - enyloxycarbony)piperazin - 1 - ylthioformimidate hydrobromide and
ethyl 4 - (2 - hydroxy - 2 - methylprop - 1 - yloxycarbonyl)piperazin - 1 - ylthio-formimidate hydrobromide

respectively. This affords:

6,7 - dimethoxy - 4 - amino - 2 - (4 - allylpiperazin - 1 - yl)quinazoline
6,7 - dimethoxy - 4 - amino - 2 - (4 - benzoylpiperazin - 1 - yl)quinazoline
6,7 - dimethoxy - 4 - amino - 2 - [4 - (3 - furoyl)piperazin - 1 - yl]quinazoline
6,7 - dimethoxy - 4 - amino - 2 - [4 - (allyloxycarbony)piperazin - 1 - yl]-quinazoline
6,7 - dimethoxy - 4 - amino - 2 - [4 - (2 - methylprop - 2 - enyloxycarbonyl)-piperazin - 1 - yl]quinazoline and
6,7 - dimethoxy - 4 - amino - 2 - [4 - (2 - hydroxy - 2 - methylprop - 1 - yloxycarbony)piperazin - 1 - yl]quinazoline,

respectively.

EXAMPLE IV

Following the procedure of Example I, and reacting ethyl 4 - (2 - hydroxy - 2 - methylprop - 1 - yloxycarbonyl)piperazine - 1 - ylformimidate with 3,4,5 - trimethoxy - 2 - aminobenzonitrile or with 3,4,5 - trimethoxy - 2 - aminobenzamidine, there is produced, in each case 6,7,8 - trimethoxy - 4 - amino - 2 - [4 - (2 - hydroxy - 2 - methylprop - 1 - yloxycarbonyl)piperazin - 1 - yl]quinazoline.

EXAMPLE V

When 4,5 - dimethoxy - 2 - aminobenzamidine hydrochloride is reacted with 1 - cyano - 4 - (2 - furoyl)piperazine, according to the procedure of Example I, the product is 6,7 - dimethoxy - 4 - amino - 2 - [4 - (2 - furoyl)piperazin - 1 - yl]-quinazoline; and when 3,4,5 - trimethoxy - 2 - aminobenzamidine hydrochloride is reacted with 1 - cyano - 4 - (2 - methylprop - 2 - enyloxycarbonyl)piperazine, also according to the procedure of Example I, the product is 6,7,8 - trimethoxy - 4 - amino - 2 - [4 - (2 - methylprop - 2 - enyloxycarbonyl)piperazin - 1 - yl]quinazoline.

EXAMPLE VI

[Q is CN; A is —C(=NH)—O—C_2H_5]

To a stirred solution of 3.56 g. (0.02 mole) of 4,5 - dimethoxy - 2 - amino-benzonitrile in 100 ml. of anhydrous benzene is added 20 ml. (0.04 mole) of a 2-molar solution of phenyllithium in 70:30 benzene:ether. The solution is stirred at ambient temperature for 15 minutes and then 5.76 g. (0.02 mole) of ethyl 4 - (2 - furoyl)-piperazine - 1 - ylformimidate hydrochloride is added. Approximately 20 ml. of solvent is distilled off, and then the remaining reaction mixture is heated under reflux for 24 hours. The bulk of the solvent is removed by evaporation *in vacuo*, and then the residue is treated cautiously with 200 ml. of water followed by 200 ml. of chloroform. The chloroform is separated off and the aqueous phase is re-extracted with chloroform. The combined organic phases are washed with water, dried using anhydrous magnesium sulphate, and then evaporated to dryness *in vacuo*. This affords crude 6,7 - dimethoxy - 4 - amino - 2 - [4 - (2 - furoyl)piperazin - 1 - yl]quinazoline.

(15)

EXAMPLE VII

[Q is CN: A is —C(=NH)—O—C_2H_5]

A solution of sodium ethoxide in ethanol is prepared by dissolving 4.6 g. (0.2 mole) of metallic sodium in 400 ml. of anhydrous ethanol. To this solution is then added 17.8 g. (0.1 mole) of 4,5 - dimethoxy - 2 - aminobenzonitrile, followed by 29.7 g. (0.1 mole) of ethyl 4 - furoylpiperazin - 1 - ylformimidate hydrochloride, at ambient temperature. The mixture is stirred for 15 minutes, and then it is heated under reflux for 16 hours. At the end of that period, the mixture is cooled to 25°C. and the ethanol is almost completely removed *in vacuo*. Ice-cold water is added to the residue, and the pH is adjusted to *ca* 6.0 by the addition of dilute hydrochloric acid. The product is filtered off and dried, giving crude 6,7 - dimethoxy - 4 - amino - 2 - (4 - furoylpiperazin - 1 - yl) - quinazoline.

EXAMPLE VIII

Following the procedure of Example VII, 4,5 - dimethoxy - 2 - aminobenzamidine hydrochloride is reacted with 1 - cyano - 4 - allylpiperazine to produce 6,7 - dimethoxy - 4 - amino - 2(4 - allylpiperazin - 1 - yl)quinazoline, and 3,4,5 - trimethoxy - 2 - aminobenzonitrile is reacted with methyl 4 - (ethoxycarbonyl)piperazin - 1 - ylthioformimidate hydroiodide to produce 6,7,8 - trimethoxy - 4 - amino - 2 - [4 - (ethoxy - carbonyl)piperazin - 1 - yl]quinazoline.

EXAMPLE IX

[Q is CN; A is —C(=NH)—O—C_2H_5]

To a stirred suspension of 3.04 g. of ethyl 4 - (2 - thienylcarbonyl) - piperazin - ylformimidate hydrochloride in 100 ml. of ethyl acetate is added 20 ml. of 40% aqueous potassium carbonate at 0°C. After stirring for a further 15 minutes, the ethyl acetate is removed, dried using anhydrous sodium sulphate, and then concentrated to dryness *in vacuo*. The residue is redissolved in 40 ml. of *N,N* - dimethylformamide, and 1.78 g. of 4,5 - dimethoxy - 2 - aminobenzo - nitrile is added. The solution is maintained at *ca* 100°C. for 20 hours, and then cooled to around 30°C. The solvent is removed *in vacuo* at this temperature to yield crude 6,7 - dimethoxy - 4 - amino - [4 - (2 - thienylcarbonyl)piperazin - 1 - yl]quinazoline.

EXAMPLE X

[Q is CN; A is —C(=NH)—S—CH_3]

A solution of 3.56 g. (0.02 mole) of 4,5 - dimethoxy - 2 - aminobenzo - nitrile and 7.82 g. (0.02 mole) of methyl 4 - benzoylpiperazin - 1 - ylthioformimidate hydroiodide in 100 ml. of *n*-butanol is heated under reflux for 20 hours. It is then cooled to ambient temperature. The solvent is removed by evaporation *in vacuo*, leaving crude 6,7 - dimethoxy - 4 - amino - 2 - (4 - benzoylpiperazin - 1 - yl)quinazoline as its hydroiodide salt.

EXAMPLE XI

When 4,5 - dimethoxy - 2 - aminobenzonitrile and 3,4,5 - trimethoxy - 2 - aminobenzonitrile, respectively are reacted with ethyl 4 - (2 - furoyl)piperazin - 1 - ylthioformimidate hydroiodide and ethyl 4 - (2 - methylprop - 2 - enyloxycarbonyl)-piperazin - 1 - ylthioformimidate hydroiodide, respectively, there are produced:

6,7 - dimethoxy - 4 - amino - 2 - [4 - (2 - furoyl)piperazin - 1 - yl] - quinazoline
and
6,7,8 - trimethoxy - 4 - amino - 2 - [4 - (2 - methylprop - 2 - enyloxy - carbonyl)-piperazin - 1 - yl]quinazoline

respectively.

EXAMPLE XII

[Q is CN; A is —C(=NH)—O—C_2H_5]

To a stirred solution of 1.78 g. (0.01 mole) of 4,5 - dimethoxy - 2 - aminobenzonitrile in 50 ml. of anhydrous ethanol is added 10 ml. of triethylamine, followed by 2.88 g. (0.01 mole) of ethyl 4 - (2 - furoyl)piperazin - 1 - ylformimidate hydrochloride. The reaction mixture is stirred at ambient temperature for 5 hours, and then it is heated under reflux for 12 hours. At this point, all the solvents are removed by evaporation *in vacuo*, and the residue is triturated under water. The solid is filtered

off and dried, yielding crude 6,7 - dimethoxy - 4 - amino - 2 - [4 - (2 - furoyl)-piperazin - 1 - yl]quinazoline.

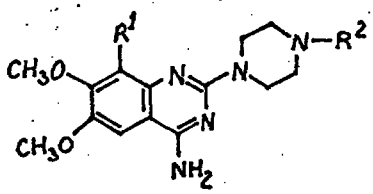
EXAMPLE XIII

[Q is —C(=NH)—NH_2; A is CN]

A solution containing 2.62 g. (0.01 mole) of 3,4,5 - trimethoxy - 2 - amino-benzamidine hydrochloride and 1.83 g. (0.01 mole) of 1 - cyano - 4 - ethoxy - carbonylpiperazine in 50 ml. of anhydrous ethanol is stirred at ambient temperature overnight. A 5-ml. aliquot of triethylamine is then added and the reaction mixture is heated under reflux for 12 hours. It is then worked up as described in Example XII, giving 6,7,8 - trimethoxy - 4 - amino - 2 - [4 - ethoxycarbonyl - piperazin - 1 - yl]quinazoline.

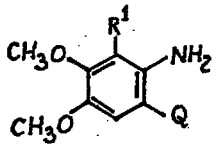
WHAT WE CLAIM IS:—

1. A process for the preparation of a quinazoline derivative having the general formula:—



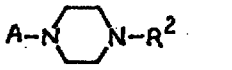
(I)

which comprises reacting a compound having the general formula:—



(II)

or a salt thereof, with a compound having the general formula:—



(III)

or a salt thereof, in a reaction-inert, organic solvent, wherein R^1 is a hydrogen atom or a methoxy group, R^2 is an alkenyl group containing three, four or five carbon atoms, a benzoyl, furoyl or thienylcarbonyl group, an alkoxycarbonyl group containing from two to five carbon atoms, an alkenyloxycarbonyl group containing four or five carbon atoms or a (2 - hydroxyalkoxy) carbonyl group containing four or five carbon atoms, Q is a cyano group or a group of the formula —C(=NH)—NH_2, and A is a cyano group or a group of the formula —C(=NH)—X—R^3, wherein X is an oxygen or sulphur atom and R^3 is an alkyl group containing one to six carbon atoms provided that when Q is a cyano group A is —C(=NH)—X—R^3.

2. A process according to claim 1, wherein the reaction is carried out at a temperature within the range of 50°C. to 180°C.

3. A process according to claim 2, wherein the reaction is carried out at a temperature within the range of 80°C. to 130°C.

4. A process according to any one of claims 1 to 3 wherein the reaction is carried out in the presence of a net excess of from 0.5 to five molar equivalents of a basic catalyst.

5. A process according to claim 4, wherein the reaction is carried out in the presence of a net excess of about one molar equivalent of the basic catalyst.

6. A process according to any one of the preceding claims wherein R^1 is a hydrogen atom and R^2 is a 2-furoyl group.

7. A process according to any one of claims 1 to 5, wherein R^1 is a methoxy group and R^2 is a 2 - methyl - 2 - hydroxyprop - 1 - yloxycarbonyl group.

8. A process according to any one of claims 1 to 5 wherein R^1 is a methoxy group and R^2 is a 2 - methylprop - 2 - enyloxycarbonyl group.

off and dried, yielding crude 6,7 - dimethoxy - 4 - amino - 2 - [4 - (2 - furoyl)-piperazin - 1 - yl]quinazoline.

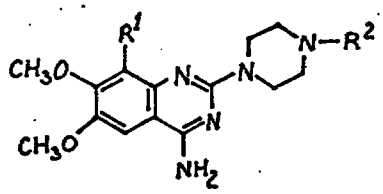
EXAMPLE XIII

[Q is —C(=NH)—NH_2; A is CN]

A solution containing 2.62 g. (0.01 mole) of 3,4,5 - trimethoxy - 2 - amino-benzamidine hydrochloride and 1.83 g. (0.01 mole) of 1 - cyano - 4 - ethoxy - carbonylpiperazine in 50 ml. of anhydrous ethanol is stirred at ambient temperature overnight. A 5-ml. aliquot of triethylamine is then added and the reaction mixture is heated under reflux for 12 hours. It is then worked up as described in Example XII, giving 6,7,8 - trimethoxy - 4 - amino - 2 - [4 - ethoxycarbonyl - piperazin - 1 - yl]quinazoline.

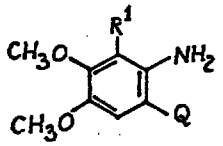
WHAT WE CLAIM IS:—

1. A process for the preparation of a quinazoline derivative having the general formula:—



(I)

which comprises reacting a compound having the general formula:—



(II)

or a salt thereof, with a compound having the general formula:—



(III)

or a salt thereof, in a reaction-inert, organic solvent, wherein R^1 is a hydrogen atom or a methoxy group, R^2 is an alkenyl group containing three, four or five carbon atoms, a benzoyl, furoyl or thienylcarbonyl group, an alkoxycarbonyl group containing from two to five carbon atoms, an alkenyloxycarbonyl group containing four or five carbon atoms or a (2 - hydroxyalkoxy) carbonyl group containing four or five carbon atoms, Q is a cyano group or a group of the formula —C(=NH)—NH_2, and A is a cyano group or a group of the formula —C(=NH)—X—R^3, wherein X is an oxygen or sulphur atom and R^3 is an alkyl group containing one to six carbon atoms provided that when Q is a cyano group A is —C(=NH)—X—R^3.

2. A process according to claim 1, wherein the reaction is carried out at a temperature within the range of 50°C. to 180°C.

3. A process according to claim 2, wherein the reaction is carried out at a temperature within the range of 80°C. to 130°C.

4. A process according to any one of claims 1 to 3 wherein the reaction is carried out in the presence of a net excess of from 0.5 to five molar equivalents of a basic catalyst.

5. A process according to claim 4, wherein the reaction is carried out in the presence of a net excess of about one molar equivalent of the basic catalyst.

6. A process according to any one of the preceding claims wherein R^1 is a hydrogen atom and R^2 is a 2-furoyl group.

7. A process according to any one of claims 1 to 5, wherein R^1 is a methoxy group and R^2 is a 2 - methyl - 2 - hydroxyprop - 1 - yloxycarbonyl group.

8. A process according to any one of claims 1 to 5 wherein R^1 is a methoxy group and R^2 is a 2 - methylprop - 2 - enyloxycarbonyl group.

* C L M S *

9. A process according to claim 1 for the preparation of a quinazoline derivative of formula (I) herein substantially as hereinbefore described with reference to the Examples.

10. Quinazoline derivatives of formula (I) herein wherever prepared by a process according to any one of the preceding claims.

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