

PATENT SPECIFICATION

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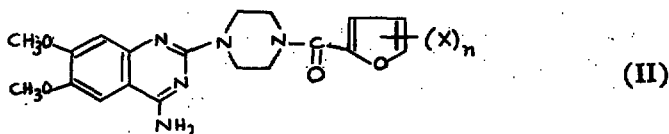


(54) CATALYTIC DEHALOGENATION PROCESS FOR PREPARING QUINAZOLINES

(71) We, PFIZER INC., a Corporation organised 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 the preparation of 2 - [4 - (2 - Furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline and certain hydrohalide salts thereof by a novel catalytic dehalogenation process from certain novel 2 - [4 - (halogenated - 2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazolines. The product is the known hypotensive agent prazosin. (See for example British Patent No. 1,156,973 and Cohen, *Journal of Clinical Pharmacology*, 10, 408 (1970)). The invention also relates to the novel 2 - [4 - (halogenated - 2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazolines which are useful as the starting materials in the above process.

The invention provides a novel process for preparing 2 - [4 - (2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline or a hydrochloride, hydrobromide or hydroiodide salt thereof which comprises contacting a compound of the formula:



wherein X is chloro, bromo or iodo and n is 1, 2 or 3, with hydrogen in the presence of a catalytic amount of a dehalogenation catalyst.

The catalyst is preferably selected from palladium, copper, cobalt, nickel or mixtures of palladium with platinum, ruthenium or rhodium. The reaction is preferably carried out in the presence of a reaction inert solvent at a temperature of from 0° to 150°C.

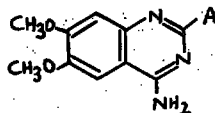
An especially preferred process is that carried out employing a compound of the formula (II) wherein n is one and X is chloro or bromo. The most preferred temperatures are from 25° to 100°C. The reaction is preferably carried out in the presence of, when n is 1 or 2, at least 1 mole, and, when n is 3, at least 2 moles of an acid acceptor having a pK_a of 7 or less. Most preferably, the reaction is carried out in the presence of a palladium catalyst, or a mixture containing from 98 to 99.9 parts by weight of palladium and from 0.1 to 2 parts by weight of platinum, ruthenium or rhodium. Most particularly preferred is the process employing 2 - [4 - (5 - bromo - 2 - furoyl) - piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline, particularly when said catalyst is palladium and said process is carried out in the presence of at least one equivalent of triethylamine as acid acceptor.

The invention also provides compounds of the formula (II) as defined above wherein X is chloro, bromo or iodo and n is 1, 2 or 3.

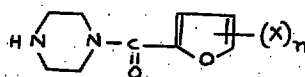
Preferred compounds are those in which n is 1 and X is chloro or bromo.

A particularly preferred starting material is 2 - [4 - (5 - bromo - 2 - furoyl)-piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline.

The invention also provides a process for preparing a compound of the formula (II) which comprises reacting a compound of the formula:

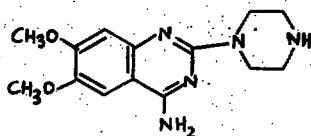


wherein A is chloro or bromo, with a compound of the formula:

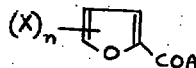


wherein X and n are as defined above.

The invention yet further provides a process for preparing a compound of the formula (II) which comprises reacting a compound of the formula:

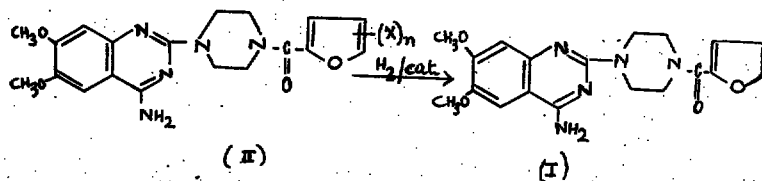


with a compound of the formula:



wherein A is chloro or bromo and X and n are as defined above.

The process of the invention may be represented as follows:—



The process is carried out by contacting the compound of formula (II) with hydrogen in the presence of a dehalogenation catalyst. By the term "dehalogenation catalyst" is meant a catalyst which will promote selective replacement of halogen with hydrogen under the conditions of the process to provide the product (I) without substantial hydrogenation or hydrogenolysis of the furan and quinazoline moieties of the starting material and product. Examples of suitable dehalogenation catalysts are noble metal catalysts such as, for example, palladium, platinum, rhenium, rhodium, ruthenium and mixtures thereof, either of the supported or nonsupported type, as well as other known catalytic compounds thereof such as the oxides, chlorides, etc. Examples of suitable catalyst supports include carbon, barium oxide, calcium carbonate and barium sulfate. These catalysts may be performed or formed *in situ* by prereduction of an appropriate oxide or salt of the catalytic compound. Prereduction is accomplished simply by suspending the catalyst precursor in the hydrogenation medium, hydrogenating it, adding the substrate and continuing the hydrogenation. Alternatively, all of the components can be incorporated at once and hydrogenation commenced. The former procedure has the advantage of permitting the operator to separately determine the quantity of hydrogen absorbed during the catalyst

prereduction and hydrogenation phase. The extent of hydrogenation can then be more readily controlled.

Further examples of suitable dehalogenation catalysts are finely divided metals such as iron, cobalt, nickel, copper and mixtures thereof. Preparation and use of such catalysts are taught in Freifelder, "Practical Catalytic Hydrogenation", John Wiley and Sons, Inc., New York, 1971, and references cited therein.

Preferred catalysts for the process of the invention are palladium, copper, cobalt, nickel and mixtures of palladium with a member selected from the group consisting of platinum, ruthenium and rhodium. While any of said mixtures containing palladium and one of said other metals in which weight ratios of palladium to platinum, ruthenium or rhodium varying over a wide range are useful in the process of the invention, especially preferred are said mixtures containing from about 98 to 99.9 parts by weight of palladium and 0.1 to 2 parts by weight of a member selected from the group consisting of platinum, ruthenium and rhodium.

The catalysts are employed in the process of the invention in "catalytic amounts", an expression well understood by those skilled in the art of hydrogenation and is illustrated in the examples appearing herein. See also, Freifelder, *loc. cit.*; pp. 79-81. Ordinarily, however, it is preferred to employ from about 1 to 40% by weight of catalyst based on the weight of starting material of formula (II).

The process of the invention is preferably carried out in the presence of a reaction inert solvent. An appropriate solvent is one which will serve to substantially dissolve or disperse the reactants and will not adversely interact with the reactants, products or catalyst. Examples of such solvents are the lower alkanols such as methanol, ethanol, isopropanol, *n*-butanol, isobutanol, isoamyl alcohol and the like; cyclic and straight chain water soluble ethers such as dioxane, tetrahydrofuran, diethylene glycol monomethylether, 2-ethoxyethanol, *N,N* - dimethylformamide, *N,N* - dimethylacetamide, as well as mixtures of such solvents with water.

The hydrogen pressure employed to carry out the process of the invention is not critical and is primarily dependent upon the apparatus utilized. In general, pressures of from atmospheric to about 2000 p.s.i. are preferred. As is known, hydrogenation at atmospheric pressure is generally carried out in equipment wherein a measured volume of hydrogen contained in a reservoir is attached to a manometer in order to measure the volume of hydrogen consumed. Alternatively, a citrate of magnesia bottle (Parr bottle) and mechanical shaker with a calibrated pressure gauge, such as a Parr hydrogenation apparatus, or a high pressure autoclave of the stirred or shaken variety may be employed.

While the dehalogenation process of the invention can be carried out over a wide range of temperature, it is preferred to employ a temperature in the range of about 0° to 150° C. An especially preferred range of temperature is from about 25° to 100° C.

When the instant process is carried out with a compound of formula (II) alone, the initial product formed is the hydrogen halide addition salt of compound (I). This may be isolated as such or may be converted to the free base by treatment with aqueous alkali such as sodium hydroxide or potassium hydroxide followed by filtration of the base or extraction into a water immiscible solvent such as ethyl ether, chloroform, methylene chloride and the like. Alternatively, the process can be carried out in the presence of an acid acceptor to directly provide the free base of compound (I) and the halide salt of the acid acceptor. By the term "acid acceptor" is meant a basic compound which when added to the reaction mixture and employed in the process of the invention, selectively reacts with the hydrogen halide released to form a salide salt without causing substantial by-product formation by further reacting with the reactant or products, and has little or no detrimental effect upon the catalyst employed. In order to successfully compete for the hydrogen halide formed during the instant process, the acid acceptor should be a stronger base than either the reactant of formula (II) or the product (I), i.e., it should be a base of pK_b of about 7 or less.

Examples of suitable acid acceptors are amines such as triethylamine, *N*-methylpyrrolidine, triethanolamine, *n*-butylamine, benzylamine, isoamylamine, morpholine and piperidine; ammonia, hydrazine and alkali metal and alkaline earth oxides and hydroxides such as those of sodium, potassium, magnesium, calcium and barium. Especially preferred as the acid acceptor for reasons of convenience, economy and efficiency is triethylamine.

The acid acceptor when present is preferably employed in an amount at least sufficient to neutralize when *n* is 1, 1 mole, or when *n* is 2 or 3, *n*-1 moles of hydrogen halide per mole of compound (II). When the amount of acid acceptor is at least equivalent to the hydrogen halide formed, the product is the free base of formula

(I). In such cases an excess of acid acceptor can be employed if desired. Alternatively, when n is 1 and no equivalents, or, when n is 2 or 3 and n-1 equivalents of the acid acceptor per mole of compound (II) is employed, the product obtained is the hydrogen halide salt of the compound of formula (I). For example, when in the starting material of formula (II), X is chloro, n is 3, and 2 equivalents of acid acceptor per mole of said compound (II) is employed, the product obtained is the hydrochloride salt of compound (I).

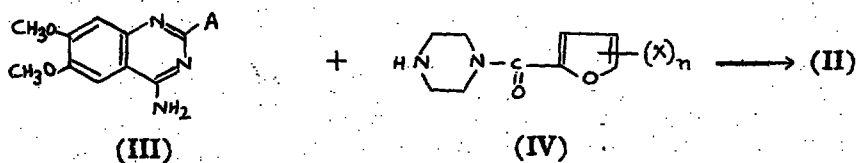
When it is desired to utilize one of said acid acceptors in the process of the invention it is preferred that at least one equivalent of acid acceptor per mole of said compound (II) is employed.

The time required for the dehalogenation process of the invention to reach substantial completion will vary according to factors such as temperature, catalyst, and the precise nature of the starting material of formula (II). Ordinarily, however, the dehalogenation will be substantially complete in from about 0.5 to 24 hours.

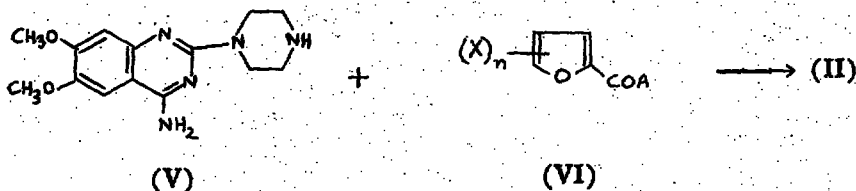
As mentioned above the product of the instant process can be either the free base of formula (I) or a hydrochloride, hydrobromide or hydroiodide salt thereof. Any of these products can be isolated and further purified, if desired, by methods well known to those skilled in the art. For example, the free base can be isolated often merely by evaporation of solvent, after removing the catalyst by filtration, whereupon the product precipitates or can be caused to precipitate by addition of a nonsolvent such as hexane or heptane. The free base can then be further purified by methods such as, for example, recrystallization or column chromatography on silica gel. When the product obtained by the process of the invention is one of the above mentioned hydrohalide salts of compound (I), it can be converted to the free base and isolated as described above, or the hydrohalide salt can be isolated by warming the reaction mixture to assure solution of said hydrogen halide salt, filtering the reaction mixture to remove catalyst, the filtrate can then be concentrated to a small volume and cooled whereupon the desired product ordinarily precipitates. It can be further purified, if desired, for example, by recrystallization.

The starting materials of formula (II), above, wherein X is chloro, bromo or iodo and n is an integer from one to three are novel compounds. They can be prepared by any of the methods known for the preparation of 2 - [4 - (2 - furoyl)piperazin-1 - yl] - 4 - amino - 6,7-dimethoxyquinazoline by employing the appropriate halogen substituted starting materials in each case. The preferred methods for preparing the compounds of formula (II) are those depicted below as Method A and Method B.

Method A



Method B



In each of the compounds of formulae (III) and (VI), A is chloro or bromo. (X)n is as described above. The compounds of formula (III) and (V) are available by methods described in U.S. 3,511,836. The acyl halides of formula (VI) are prepared from the corresponding halogenated-2-furoic acids by well-known methods, for example by reacting said acids with an excess of thionyl chloride or thionyl bromide followed by evaporation of the reaction mixture. Of the halogenated furoic acids from which the compounds (VI) are derived, 5-bromo-2-furoic acid is commercially

available. The remaining chloro and bromofuroic acids are prepared by methods described by Shepard *et al.*, *Jour. Amer. Chem. Soc.*, 52, 2083 (1930) and Gilman *et al.*, *ibid.*, 57, 1146 (1935) and reference cited therein. The iodofuroic acids are prepared from the corresponding iodofurfurals by oxidation with alkaline peroxide by the method of Borisova *et al.*, *Chem. Abstr.*, 73, 35134f (1970) or by the method of Sornay *et al.*, *Bull. Soc. Chem., France*, 990 (1971).

When Method A is employed, the 1-substituted piperazine of formula (IV), which can be prepared from the above-described acid halides of formula (VI) and an equimolar amount of piperazine, and the quinazoline (III) are typically combined in approximately equimolar amounts in the presence of a reaction inert organic solvent. The reaction can be carried out over a wide range of temperature, however, temperatures in the range of about 50° to 150° C. are preferred. The reaction is ordinarily complete in from about 1 to 24 hours. The product may be isolated in the form of the hydrochloride or hydrobromide salt and subsequently converted to the free base of formula (II) by standard methods. Alternatively, the reaction mixture can be made alkaline, for example, with sodium hydroxide or potassium hydroxide and the free base isolated by extraction and evaporation of solvent. Examples of suitable reaction inert solvents for this method are the alkanols such as ethanol, *n*-butanol, isoamyl alcohol, *n*-hexanol and cyclohexanol; *N,N* - dimethylformamide, *N,N* - dimethylacetamide, dimethylsulfoxide, diethyleneglycol diethyl ether, ethyleneglycol-*n*-butyl ether, chloroform and methylene chloride.

When Method B is employed the compound of formula (V) and e.g. an equimolar amount of compound of formula (VI) are typically reacted in the presence of a suitable reaction inert organic solvent. The reaction is preferably carried out at temperatures of from about -20° to 100° C. Examples of suitable solvents for use in this method are those set forth above for Method A. The reaction is ordinarily complete in from about a few minutes to ten hours. The desired product is isolated by standard methods, such as, for example, adjusting the reaction mixture to an alkaline pH by addition of an aqueous base, for example, sodium hydroxide, potassium hydroxide or sodium carbonate, extracting the product with a water immiscible solvent such as chloroform or methylene chloride and evaporation of the solvent.

For reasons of economy and efficiency especially preferred compounds of formula (II) are those wherein *n* is one and X is chloro or bromo. Most particularly preferred is 2-[4-(5-bromo-2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethylquinazoline.

The following examples are provided to illustrate the invention.

EXAMPLE 1.

2-[4-(5-Bromo-2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline

To a flask containing 19.1 g. (0.10 mole) of 5-bromo-2-furoic acid in 100 ml. of chloroform was added 20 g. of thionyl chloride and the resulting mixture was stirred at room temperature for 2 hours then allowed to stand overnight. The volatile components were then evaporated *in vacuo* to obtain 5-bromo-2-furoyl chloride. This was dissolved in 50 ml. of methylene chloride and the solution added dropwise at 25° C. to a solution of 8.6 g. (0.10 mole) of piperazine in 50 ml. of the same solvent. The addition required about 30 minutes. The resulting mixture was allowed to stir for another hour then made alkaline by addition of 2N sodium hydroxide solution. The organic layer was separated and the aqueous layer was extracted again with methylene chloride. The organic layers were dried over anhydrous potassium carbonate then evaporated to dryness to obtain 23 g. of 1-(5-bromo-2-furoyl)piperazine. A portion was crystallized from methylene chloride-ethyl acetate, M.P. 113—115° C.

Anal. Calc'd. for $C_{20}H_{21}O_2N_5Br$: C, 41.72; H, 4.28; N, 10.81; Br, 30.84
Found: C, 41.44; H, 4.35; N, 10.66; Br, 30.49

EXAMPLE 1 (Continued).

In a reaction vessel was placed, 9.55 g. (0.04 mole) of 4-amino-2-chloro-6,7-dimethoxyquinazoline, prepared by the procedure of U.S. 3,511,836, 200 ml. of isoamyl alcohol and 20.7 g. (0.08 mole) of the 1-(5-bromo-2-furoyl)piperazine obtained above. The resulting suspension was heated at reflux for 90 minutes, then cooled, filtered and washed with ethanol to obtain 21.8 g. of crude hydrochloride salt of the title compound which melted with decomposition at 276—278° C. This was slurried in 200 ml. of ethanol and 2N sodium hydroxide solution was added to effect solution. The solution was concentrated to a small volume by evaporation *in vacuo*, chilled, filtered, washed with water and dried to obtain 18.8 g. of product, M.P.

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206—209° C. This was dissolved in a mixture of chloroform and methanol, dried over sodium sulfate, carbon treated and the solvent replaced with ethyl acetate. Upon crystallization 9.8 g. (53%) of purified product was obtained, M.P. 213—215° C.

Anal. Calc'd for $C_{19}H_{20}N_4O_4Br$: C, 49.36; H, 4.36; N, 15.15; Br, 17.28
Found: C, 48.70; H, 4.36; N, 14.87; Br, 16.87

EXAMPLE 2.

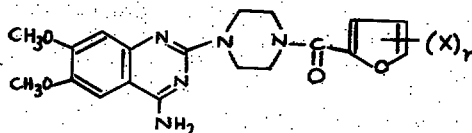
2-[4-(3-Chloro-2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline
3-chlorofuran-2-carboxylic acid, prepared by the method of Shepard *et al.*, is reacted at room temperature with excess thionyl chloride followed by evaporation *in vacuo* to obtain the acid chloride as a residue.

To a solution of 28.9 g. (0.10 mole) of 2 - (1 - piperazinyl) - 4 - amino - 6,7-dimethoxyquinazoline, prepared as described in U.S. 3,511,836, in 300 ml. of methanol is added with vigorous stirring, 16.5 g. (0.10 mole) of the above acid chloride over 30 minutes and the resulting mixture stirred for an additional three hours at room temperature. The solvent is removed *in vacuo* and the residue is slurried with methylene chloride and made alkaline with 2N sodium hydroxide solution. The organic layer is separated, dried over sodium sulfate and evaporated to dryness to obtain the title compound.

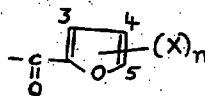
When thionyl bromide is employed in place of thionyl chloride in the above procedure and the acid bromide obtained is reacted with 2 - (1 - piperazinyl) - 4-amino - 6,7 - dimethoxyquinazoline, the results are substantially the same.

EXAMPLE 3.

When the procedure of Example 1 or Example 2 is repeated but with the acid chloride used therein replaced with the appropriate halo-2-furoyl chloride or halo-2-furoyl bromide, the following compounds are similarly obtained.



Procedure of
Example No.



1	3-chloro-2-furoyl
1	4-chloro-2-furoyl
1	3,4-dichloro-2-furoyl
2	3,4,5-trichloro-2-furoyl
2	3-bromo-2-furoyl
2	4-bromo-2-furoyl
2	5-bromo-2-furoyl
1	4,5-dibromo-2-furoyl
1	5-iodo-2-furoyl
2	4-iodo-2-furoyl

EXAMPLE 3 (Continued)

The 2-furoyl chlorides or bromides are prepared from the corresponding halo-2-furoic acids. The chloro and bromofuroic acids are prepared by methods described by Shepard *et al.*, *Jour. Amer. Chem. Soc.*, 52, 2083 (1930) and Gilman *et al.*, *ibid.*, 57, 1146 (1935) and reference therein. The iodofuroic acids are prepared from the corresponding iodofurfural by oxidation with alkaline peroxide by the method of Borisova *et al.*, *Chem. Abstr.*, 73, 35134f (1970) or by the method of Sornay *et al.*, *Bull. Soc. Chem., France*, 990 (1971).

EXAMPLE 4.

In a Paar pressure bottle is placed 1.0 g. (2.16 mmole) of 2 - [4 - (5 - bromo - 2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline, 10 ml. of methanol, 1.0 ml. of triethylamine and 0.4 g. of 5% Pd-on-carbon (50% wet). The bottle was placed in a Paar shaker and pressurized with hydrogen to 50 p.s.i. at room temperature. After shaking for 18 hours the theoretical amount of hydrogen was taken up. The mixture of catalyst and precipitated product was filtered and the solids were slurried in 25 ml. of chloroform and filtered again to remove catalyst. To the filtrate was added 50 ml. of hexane, the mixture stirred for ten minutes then filtered to obtain a crude product which was purified on an 18 × 3 inch column of silica gel, eluting with ethyl acetate-diethylamine (90:10 by volume) to obtain 300 mg. of 2 - [4 - (2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline, M.P. 266° C. which was identified by comparison of the infrared spectrum in chloroform with that of an authentic sample, and by thin layer chromatography on silica gel.

EXAMPLE 5.

In an atmospheric hydrogenation apparatus flask is placed 4.18 g. (0.01 mole) of 2 - [4 - (3 - chloro - 2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline, 75 ml. of 95% ethanol, 0.50 g. (0.10 mole) of hydrazine hydrate and 0.5 g. of a catalyst containing 98 parts by weight of palladium and 2 parts by weight of platinum. The resulting mixture is cooled to 0° C. and exposed to hydrogen at atmospheric pressure for 4 hours. The mixture is then filtered to remove catalyst, the filtrate concentrated *in vacuo* to dryness then partitioned between methylene chloride and water. The organic layer is dried over sodium sulfate and evaporated to dryness to obtain the 2 - [4 - (2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline which is purified by silica gel column chromatography.

When the above procedure is repeated but employing 0.5 g. of catalyst containing 99.9 parts by weight of palladium and 0.1 part by weight of platinum, the results are essentially unchanged.

EXAMPLE 6.

In a 500 ml. autoclave is placed 9.24 g. (0.02 mole) of 2 - [4 - (4 - bromo - 2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline, 2.0 g. of 50% wet Raney nickel catalyst and 200 ml. of 70% ethanol (7:3 ethanol/water, by weight). The mixture is maintained at 100° C. and 200 p.s.i. hydrogen pressure for 30 minutes then cooled to room temperature. The catalyst is removed by filtration and the filtrate concentrated to remove ethanol, the concentrate is made alkaline with potassium carbonate, extracted with chloroform and the extracts concentrated to dryness to obtain 2 - [4 - (2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline. The product can be purified further by silica gel column chromatography.

EXAMPLE 7.

In an atmospheric hydrogenation flask is placed 4.18 g. (0.01 mole) of 2 - [4 - (4 - chloro - 2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline 200 ml. of isoamyl alcohol and 0.20 grams of a powdered catalyst containing 99.9 parts of palladium and 0.1 part of rhodium by weight. The resulting mixture is hydrogenated at atmospheric pressure for 2 hours with vigorous stirring. The theoretical amount of hydrogen is consumed. The mixture is then disconnected from the apparatus, heated to boiling and filtered while hot to remove the catalyst. The filtrate is cooled in ice, then filtered to obtain 2 - [4 - (2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline hydrochloride.

When the above procedure is repeated, but employing 0.01 mole of 2 - [4 - (5 - bromo - 2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline in place of the corresponding 4-chloro-2-furoyl congener used above, 2 - [4 - (2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline hydrobromide is similarly obtained.

13

EXAMPLE 8

When the indicated halogen containing starting material selected from the products obtained in Examples 1 through 3, are subjected to the conditions tabulated below 2-[4-(2-furoyl)piperazin-1-yl]-4-amino-6,7-dimethoxyquinazoline is obtained either as the free base or as the indicated hydrohalide salt.

Starting Material	Reaction Conditions						Product Isolated	
	Moles	Catalyst (Grams)	Temp., °C.	Time, Hours	Solvent*	Acid Acceptor (Moles)		Hydrogen Pressure p.s.i.
	0.10	5% Pd/C (2)	100°	3	Dioxane	TEA (0.10)	15	HCl salt
	0.05	10% Pd/C (0.8)	150°	2	Isoamyl alcohol	TEA (0.15)	100	Free base
	0.05	99% Palladium 0.1% Ruthenium (w/w) (0.2)	35°	10	Ethanol water 7:3 (w/w)	MgO (0.05)	50	Free base
	0.10	99% Palladium 1% Rhodium (w/w) (0.5)	25°	12	Methanol	Ammonia (0.20)	15	Free base
	0.05	Copper powder (1)	50°	4	Methanol	Ba(OH) ₂ (0.20)	15	Free base
	0.02	Raney cobalt 50% (1)	25°	6	n-Butanol	None	15	HI salt
	0.01	Pd/Ru 98:2 (w/w) (0.1)	25°	5	THF	N-methyl pyrrolidine (0.02)	15	Free Base

EXAMPLE 8 (Continued)

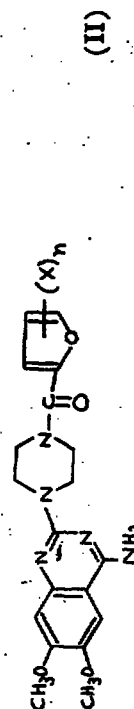
Starting Material		Reaction Conditions						Product Isolated
	Moles	Catalyst (Grams)	Temp., °C.	Time Hours	Solvent*	Acid Acceptor [†] (Moles)	Hydrogen Pressure p.s.i.	
								
5-Iodo-2-furoyl	0.01	Pd/Rh 98:2 (w/w) (0.1)	25°	6	Ethanol	None	100	HI salt
5-Bromo-2-furoyl	0.10	5% Pd/c (1.5)	25°	10	DMF-H ₂ O 8:2 (w/w)	CaO (0.05)	2000	Free base
5-Chloro-2-furoyl	0.10	Raney Cobalt- Raney Copper 1:1 (w/w) (1.0)	25°	8	Ethanol- water 7:3 (w/w)	NaOH (0.10)	15	Free base

* THF is tetrahydrofuran, DMF is N,N-dimethylformamide

† TEA is triethylamine

WHAT WE CLAIM IS:—

1. A process for preparing 2 - [4 - (2 - furoyl)piperazin - 1 - yl] - 4 - amino-6,7 - dimethoxyquinazoline or a hydrochloride, hydrobromide or hydroiodide salt thereof which comprises contacting a compound of the formula:



wherein X is chloro, bromo or iodo and n is 1, 2 or 3, with hydrogen in the presence of a catalytic amount of a dehalogenation catalyst.

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2. A process as claimed in claim 1, wherein said catalyst is palladium, copper, cobalt, or nickel or a mixture of palladium with platinum, ruthenium or rhodium, and which is carried out in the presence of a reaction inert solvent at a temperature of from 0° to 150°C.

3. A process as claimed in claim 2, wherein said contacting is carried out at a temperature of from 25° to 100°C.

4. A process as claimed in claim 2 or 3 wherein said contacting is carried out in the presence of when n is 1, at least 1, and, when n is 2 or 3, at least n-1 moles of an acid acceptor which has a pK_a of 7 or less.

5. A process as claimed in claim 4 wherein at least one equivalent of the acid acceptor per mole of the compound of the formula (II) is employed.

6. A process as claimed in claim 4 or 5 wherein the acid acceptor is triethylamine.

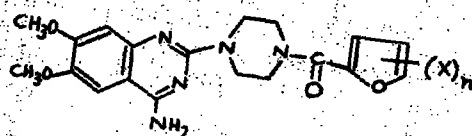
7. A process as claimed in any one of claims 2 to 6 wherein the catalyst is palladium.

8. A process as claimed in any one of claims 2 to 6 wherein the catalyst is a mixture containing from 98 to 99.9 parts by weight of palladium and from 0.1 to 2 parts by weight of platinum, ruthenium or rhodium.

9. A process as claimed in any one of claims 2 to 8 wherein n is one and X is chloro or bromo.

10. A process as claimed in claim 9 wherein the compound of the formula (II) is 2 - [4 - (5 - bromo - 2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline.

11. A compound of the formula:



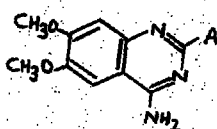
(II)

wherein X is chloro, bromo, or iodo and n is 1, 2 or 3.

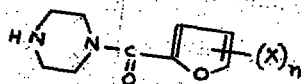
12. A compound as claimed in claim 11 wherein n is 1 and X is chloro or bromo.

13. 2 - [4 - (5 - Bromo - 2 - furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxyquinazoline.

14. A process for preparing a compound of the formula (II) as claimed in claim 11 which comprises reacting a compound of the formula:

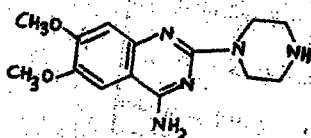


wherein A is chloro or bromo, with a compound of the formula:



wherein X and n are as defined in claim 11.

15. A process for preparing a compound of the formula (II) as claimed in claim 11 which comprises reacting a compound of the formula:





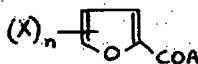
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with a compound of the formula:



wherein A is chloro or bromo and X and n are as defined in claim 11.

5 16. A process as claimed in claim 14 substantially as hereinbefore described in Example 1 or 3.

17. A process as claimed in claim 15 substantially as hereinbefore described in Example 2 or 3.

10 18. A compound of the formula (II) as claimed in claim 11 which has been prepared by a process as claimed in any one of claims 14 to 17.

19. A process as claimed in claim 1 substantially as hereinbefore described in any one of Examples 4 to 8.

20. 2 - [4 - (2 - Furoyl)piperazin - 1 - yl] - 4 - amino - 6,7 - dimethoxy-quinazoline or a hydrochloride, hydrobromide or hydroiodide salt thereof which has been prepared by a process as claimed in any one of claims 1 to 10 and 19.

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