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3,560,501

PROCESS FOR MAKING DIHYDROQUINAZOLINES

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Int. Cl. C07d 51/48
U.S. Cl. 260—251 1 Claim

ABSTRACT OF THE DISCLOSURE

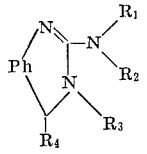
2-hydroxy- or mercapto-4-aryl-quinazolines, or the esters or ethers thereof, can be partially reduced with alkali or alkaline earth metal borohydrides, to form the corresponding 3,4-dihydro derivatives, which are valuable intermediates in the preparation of pharmacologically active 2-amino derivatives thereof.

SUMMARY OF THE INVENTION

The present invention concerns and has for its object the provision of 2-amino-4-aryl-3,4-dihydroquinazolines and methods for their preparation.

DESCRIPTION OF THE PREFERRED EMBODIMENT

More particularly it relates to compounds having the Formula I



(I)

in which Ph stands for a 1,2-phenylene radical, each of R_1, R_2 and R_3 for hydrogen or an aliphatic hydrocarbon radical and R_4 for a carbocyclic or heterocyclic aromatic radical, acyl derivatives thereof and salts of these compounds.

The 1,2-phenylene radical Ph may be unsubstituted or substituted by one or more than one of the same or different substituents attached to any of the positions available for subsitution. Such substituents are, for example, lower alkyl, such as methyl, ethyl, n- or i-propyl or butyl, etherified hydroxy or mercapto, for example lower alkoxy or alkylmercapto, such as methoxy, ethoxy, n- or i-propoxy or butoxy, methyl- or ethyl-mercapto, esterified hydroxy, for example halogeno, such as fluoro, chloro or bromo, trifluoromethyl or nitro. Preferred 1,2-phenylene radicals Ph are 1,2-phenylene, (lower alkyl)-1,2-phenylene, (lower alkoxy)-1,2-phenylene, (lower alkyl-mercapto)-1,2-phenylene, (halogeno)-1,2-phenylene, (trifluoromethyl)-1,2-phenylene and (nitro)-1,2-phenylene.

An aliphatic radical R_1, R_2 and R_3 represents especially lower alkyl, e.g., methyl, ethyl, n- or i-propyl, n-, i-, sec. or tert. butyl, n-pentyl, n-hexyl or n-heptyl. It may also stand for lower alkenyl, such as allyl or methallyl, cycloalkyl or cycloalkyl-lower alkyl having from three to eight, especially from five to seven, ring-carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, cycloheptyl or cyclooctyl, cyclopropylmethyl, cyclopentylmethyl, 2-cyclopentylethyl, cyclohexylmethyl, 1-cyclohexylethyl or cycloheptylmethyl, as well as for monocyclic carbocyclic aryl-lower alkyl, such as benzyl, 1- or 2-phenylethyl. These radicals may contain additional substituents, especially in the aromatic portion, such as those mentioned for Ph.

They also may be interrupted by hetero atoms, preferably by one oxygen, sulfur and/or nitrogen atom. Such radicals are, for example lower alkoxy-lower alkyl, such as methoxymethyl, ethoxymethyl, n-propoxymethyl, 1- or 2-methoxy-, ethoxy or i-propoxy-ethyl, 1-, 2- or 3-methoxy-, ethoxy- or n-propoxy-propyl or 4-tert. butoxybutyl, the corresponding phenoxy-lower alkyl and lower alkylmercapto-lower alkyl groups, mono- or di-lower alkylamino-lower alkyl, lower alkyleneimino-lower alkyl or aza-, oxa- or thia-alkyleneimino-lower alkyl or N-phenyl-aza-alkyleneimino-lower alkyl groups with preferably 4 to 6 ring-carbon atoms and in which latter the hetero-atom is preferably separated from the ring-nitrogen atom by at least two carbon atoms, such as 2-methylamino-, 2-dimethylamino- or 2-diethylamino-ethyl, 3-dimethylamino- or 3-diethylamino-propyl, 2-pyrrolidino-ethyl, 3-piperidino-propyl, 2-piperazino-ethyl, 2-(4-methyl-piperazino)-ethyl, 3-(4-ethyl-piperazino)-propyl, 2-(4-phenyl-piperazino)-propyl, 2-(4-phenyl-piperazino)-ethyl, 2-morpholino-ethyl or 3-thiamorpholino-propyl.

R_1 and R_2, when taken together, may also represent lower alkylene, aza-, oxa- or thia-alkylene or N-phenyl-aza-alkylene, such as 1,2-ethylene, 1,4-butylene, 1,4- or 1,5-pentylene, 3-methyl-1,5-pentylene, 2,5- or 1,6-hexylene or 2,6-heptylene; 3-aza-1,5-pentylene, 3-methyl, ethyl or phenyl-3-aza-1,5-pentylene, 3-oxa or thia-1,5-pentylene.

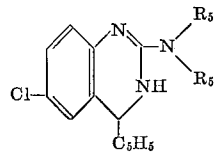
An aromatic radical R_4 particularly stands for mono- or bicyclic carbocyclic aryl, i.e., phenyl, 1- or 2-naphthyl, or heterocyclic aryl, such as furyl, thienyl or pyridyl. Said aryl groups may contain one or more than one of the same or different substituents attached to any position available for substitution, for example those mentioned for Ph. R_4 stands primarily for phenyl, (lower alkyl)-phenyl, (lower alkoxy)-phenyl, (lower alkylmercapto)-phenyl, (halogeno)-phenyl, (trifluoromethyl)-phenyl, (nitro)-phenyl, pyridyl, (lower alkyl)-pyridyl, thienyl or (lower alkyl)-thienyl.

The acyl derivatives are particularly those of carboxylic acids, preferably aliphatic, araliphatic or aromatic carboxylic acids, such as those mentioned below, especially of lower alkanoic acids, such as acetic, propionic, butyric or pivalic acid.

The compounds of this invention have useful pharmacological properties. Apart from analgesic and central nervous depressing effects, they exhibit primarily antiinflammatory activity, as can be demonstrated in animal tests using, for example, rats as test objects. They are, therefore, useful as antiinflammatory agents, preferably for oral application, in place of corticosteroids, such as cortisone or hydrocortisone, in the treatment of tissue inflammations, such as arthritic inflammations and similar conditions. Furthermore, they are valuable intermediates for the preparation of other useful products, particularly of pharmacologically active compounds. Thus the corresponding 2-amino-4-aryl-quinazolines disclosed in copending application Ser. No. 579,511, filed Sept. 15, 1966 now Pat No. 3,509,141 issued Apr. 28, 1970 are obtained from the compounds of this invention by dehydrogenation.

Particularly useful are compounds of the Formula I in which Ph stands for 1,2-phenylene, (lower alkyl)-1,2-phenylene, (lower alkoxy)-1,2-phenylene or (halogeno)-1,2-phenylene, each of R_1 and R_3 for hydrogen or lower alkyl, R_2 for hydrogen, lower alkyl, amino-lower alkyl, mono- or di-lower alkylamino-lower alkyl, lower alkyleneimino-lower alkyl, lower aza-, oxa- or thiaalkyleneimino-lower alkyl, R_1 and R_2, when taken together also stand for lower alkylene or lower aza-, oxa- or thiaalkylene and R_4 for phenyl, (lower alkyl)-phenyl, (lower alkoxy)-phenyl or (halogeno)-phenyl, and acid addition salts thereof.

Especially mentioned are those compounds of the Formula II

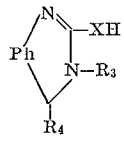


(II)

in which R_5 stands for hydrogen, methyl or ethyl and R_6 for methyl, ethyl or 2-dimethylamino-ethyl or R_5 and R_6 together for 1,4-butylene, 1,5-pentylene, 3-methyl-3-aza-1,5-pentylene or 3-oxa-1,5-pentylene, and therapeutically acceptable acid addition salts thereof, which, when given orally to rats at doses between about 5 and 50 mg./kg./day, preferably between about 10 and 25 mg./kg./day, show outstanding antiinflammatory effects according to the grandulama pouch or carrageenin paw test.

The compounds of this invention are prepared according to known methods. For example, the process for their preparation consists in

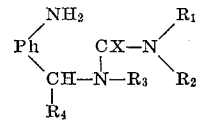
(a) Reacting a 2-hydroxy or mercapto-4-aryl-3,4-dihydroquinazoline, more particularly such of the Formula III



(III)

in which X stands for oxygen or sulfur, or preferably a reactive ester or ether thereof, with ammonia or an amine, preferably that of the formula R_1—NH—R_2, or

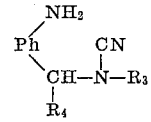
(b) Condensing an N-(α-aryl-2-aminobenzyl)-urea or thiourea, more particularly such of the Formula IV



(IV)

or ethers thereof, or

(c) Condensing an N-(α-aryl-2-aminobenzyl)-cyanamide, more particularly such of the Formula V



(V)

and, if desired, converting any compound obtained into another disclosed compound.

A reactive ester of the 2-hydroxy-4-aryl-3,4-dihydroquinazoline, more particularly is such of a hydrohalic or sulfonic acid, such as hydrochloric, hydrobromic, methane-, ethane-, benzene- or p-toluenesulfonic acid. An ether of the compounds mentioned under items (a) and (b) is preferably a lower alkyl ether of the 2-hydroxy or mercapto-4-aryl-3,4-dihydroquinazoline of the corresponding N-(α-aryl-2-aminobenzyl)isourea or isothiourea. In the condensation according to (b) any water, alcohol or mercaptan formed may either be distilled off aceotropically or absorbed by a condensing agent, such as a carbodiimid.

The compounds obtained according to said process may be converted into other disclosed compounds by methods in themselves known. Thus, for example, into any primary, or secondary amino nitrogen atom, for example into compounds of Formula I in which R_1, R_2 and/or R_3 stands for hydrogen, a substituent may be introduced, if necessary, after conversion of the compound obtained into a metal, e.g. alkali metal, derivative thereof. This can be done, for example, by reaction with a reactive ester of an appropriate alcohol, for example, that

of a hydrohalic, e.g. hydrochloric, hydrobromic or hydriodic acid, or a sulfonic acid, such as a lower alkane or benzene sulfonic acid, e.g. those mentioned above, or an aryl diazonium salt, whereby higher substituted amines are obtained, or by reductive alkylation, i.e. reaction with an appropriate oxo-compound and subsequent reduction. In compounds, amino-substituted by radicals which can be eliminated, for example, amino-substituted by α-arylalkyl, e.g. benzyl, or phthaloyl radicals, the said radicals can be split off in the usual manner by hydrogenolysis or hydrazinolysis.

The above-mentioned reactions are carried out according to standard methods, in the presence or absence of diluents, preferably such as are inert to the reagents and are solvents thereof, of catalysts, condensing agents and/or inert atmospheres, at low temperatures, room temperature or elevated temperatures, at atmospheric or superatmospheric pressure. Condensing agents are especially used in the reaction with said reactive esters in order to eliminate the acid formed. They are basic agents, for example, alkali or alkaline earth metal carbonates or lower alkoxides, or more especially, organic bases such as pyridine or collidine, but particularly aliphatic tertiary amines, such as a tri-lower alkylamine, e.g. triethylamine.

The compounds of the invention are obtained in the free form or in the form of their salts, depending on the conditions under which the process is carried out; the salts are also included in the present invention. Salts that are obtained can be converted into the free bases in known manner, for example, with alkalis or ion exchangers. Free bases that are obtained can be converted into salts by reaction with inorganic or organic acids, especially those that are suitable for the formation of therapeutically useful salts. Such acids are, for example, hydrohalic acids, e.g. hydrochloric or hydrobromic acid, sulfuric, phosphoric, nitric or perchloric acid, aliphatic, alicyclic, araliphatic, aromatic, or heterocyclic carboxylic or sulfonic acids, for example, formic, acetic, propionic, succinic, glycollic, lactic, malic, tartaric, citric, ascorbic, maleic, hydroxymaleic, pyroracemic, phenylacetic, benzoic, 4-aminobenzoic, anthranilic, 4-hydroxybenzoic, salicylic, aminosalicylic, embonic, nicotinic, methanesulfonic, hydroxyethanesulfonic, ethylenesulfonic, halogenbenzenesulfonic, toluenesulfonic, naphthalenesulfonic and sulfanilic acid; methionine, tryphophan, lysine and arginine.

These or other salts of the new compounds, for example, the picrates, can also be used for purification of the bases obtained; the bases are converted into salts, the salts are separated and the bases are liberated from the salts. In view of the close relationship between the free compounds and the compounds in the form of their salts, whenever a free base is referred to in this context, a corresponding salt is also intended, provided such is possible or appropriate under the circumstances.

The invention further includes any variant of the present process, in which an intermediate product obtainable at any stage of the process is used as starting material and any remaining steps are carried out, or the process is discontinued at any stage thereof, or in which the starting materials are formed under the reaction conditions, or in which the reaction components may be used in the form of their salts. Mainly, those starting materials should be used in the reaction of the invention that lead to the formation of those compounds indicated above as being specially valuable.

The starting material used in reaction (a) is prepared from the corresponding 2-hydroxy- or mercapto-4-aryl-quinazolines, or the esters or ethers thereof, disclosed in the above-mentioned copending application by partial reduction with the use of alkali metal or alkaline earth metal borohydrides, such as sodium borohydride. This process is new and is considered to be included within the scope of the present invention. The starting material used in reaction (b) may be obtained from corresponding α-

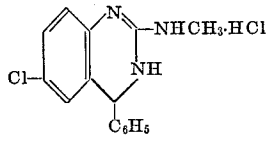
aryl-2-aminobenzylamines by reaction with isocyanates or thiocyanates or carbamic acid halides, or by solivolysis of corresponding cyanamides. The latter, i.e. the starting material used in reaction (c), may be obtained by reacting said α-aryl-2-aminobenzylamines with cyanogen halides. These starting materials may be formed as intermediates under the reaction conditions for the formation of the final products.

The compounds of this invention are useful in the form of compositions for enteral, parenteral or topical administration which contain a pharmacologically effective amount of the compounds of this invention in admixture with a pharmaceutically acceptable, organic or inorganic, solid or liquid carrier, which usually represents the major portion of the pharmaceutical composition. For making up the latter, there are employed carrier materials suitable for the preparation of pharmaceutical compositions, such as water, gelatine, sugars, e.g. lactose, glucose or sucrose, starches, e.g. corn starch, wheat starch or rice starch, stearic acid or salts thereof, e.g. calcium or magnesium stearate, talc, vegetable oils, alcohol, e.g. ethanol, benzyl alcohol or cetyl alcohol, petrolatum, gums, acacia, propylene glycol, polyalkylene glycols or any other known carrier for pharmaceutical compositions. The pharmaceutical preparations may be in solid form, e.g. capsules, tablets or dragees, in liquid form, e.g. solutions or suspensions, or in the form of emulsions, e.g. salves or creams. If desired, they may contain auxiliary substances, such as preserving, stabilizing, wetting, emulsifying or coloring agents, salts for varying the osmotic pressure or buffers, The above preparations are prepared according to standard methods used for the manufacture of pharmaceutically acceptable compositions which, if desired, also contain, in combination, other physiologically useful substances.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centrigrade and all parts wherever given are parts by weight.

EXAMPLE 1

2.5 g. 2,6-dichloro-4-phenyl-3,4-dihydro-quinazoline are dissolved in 140 ml. saturated methanolic methylamine and the solution is refluxed for 3½ hours. It is then evaporated on the steam cone and the residue triturated first with 100 ml. diethyl ether, then with 10 ml. water and recrystallized from aqueous ethanol to yield the 2-methylamino-4-phenyl-6-chloro-3,4-dihydroquinazoline hydrochloride of the formula



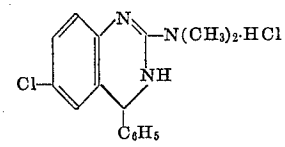
melting at 249–251° with decomposition.

The starting material is prepared as follows: To the stirred suspension of 29.0 g. 2,6-dichloro-4-phenyl-quinazoline in 800 ml. methanol, 40.0 g. sodium borohydride are added portion-wise during 40 minutes. After the foaming has subsided nearly all of the material is dissolved. The reaction mixture is filtered, the filtrate concentrated to about 500 ml. at the steam cone and the concentrate poured into 2.5 liter water. The precipitate formed is filtered off, washed with water and dissolved in about 2.5 liter diethyl ether. The solution is washed 3 times with water, dried, filtered and evaporated. The residue is recrylstalized from diethyl ether and dried in vacuo to yield the 2,6-dichloro-4-phenyl-3,4-dihydro-quinazoline melting at 164–166°.

In the analogous manner the 2-isopropylamino-4-phenyl-6-chloro-3,4-dihydro-quinazoline hydrochloride is obtained.

EXAMPLE 2

4.0 g. 2,6-dichloro-4-phenyl-3,4-dihydro - quinazoline are treated with 90 ml. anhydrous dimethylamine and the resulting solution is allowed to evaporate overnight. The residue is dissolved in 25 ml. ethanol and the product precipitated with diethyl ether. It is filtered off and recrystallized from water to yield the 2-dimethylamino-4-phenyl-6-chloro-3,4-dihydroquinazoline hydrochloride of the formula



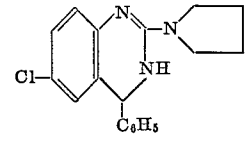
melting at 307–309° with decomposition.

1.0 g. thereof is dissolved in 100 ml. warm water and the solution made basic with sodium hydroxide. The precipitate formed is filtered off, washed with water, recrystallized from diethyl ether and dried at 65° to yield the corresponding base melting at 163–165°.

In the analogous manner the 2-diethylamino-4-phenyl-6-chloro-3,4-dihydro - quinazoline hydrochloride is obtained.

EXAMPLE 3

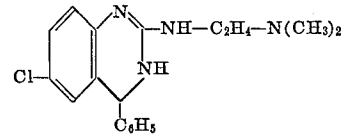
4.0 g. 2,6-dichloro-4-phenyl-3,4-dihydro - quinazoline are dissolved in 35 ml. pyrrolidine and the solution allowed to stand at room temperature for 2 days. It is then evaporated on the steam cone, the residue triturated with water and recrystallized from ethanol to yield the 2-pyrrolidino-4-phenyl-6-chloro-3,4-dihydro-quinazoline of the formula



melting at 178–180°.

EXAMPLE 4

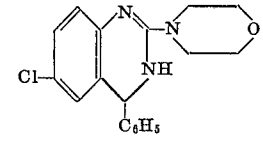
The mixture of 4.0 g. 2,6-dichloro-4-phenyl-3,4-dihydro-quinazoline and 4.0 g. 2-dimethylamino-ethylamine is heated at the steam cone for 2 hours and the excess amine evaporated. The residue is triturated with ethanol and diethyl ether and recrystallized from ethanol-diethyl ether to yield as fraction A the 2-(2 - dimethylamino-ethylamino)-4-phenyl-6-chloro-3,4-dihydro-quinazoline of the formula



melting at 153–154° after another recrystallization from diethyl ether. The smaller fraction B represents the corresponding dihydrochloride, which melts after another recrystallization from ethanol-diethyl ether at 280–281°.

EXAMPLE 5

The mixture of 3.0 g. 2,6-dichloro-4-phenyl-3,4-dihydro-quinazoline and 25 ml. morpholine is heated at the steam cone for 2 hours. Hereupon it is evaporated, the residue triturated with water and recrystallized from ethanol to yield the 2-morpholino-4-phenyl-6-chloro-3,4-dihydro-quinazoline of the formula

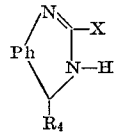


melting at 198–200°.

Replacing the morpholine by the same amount of 1-methyl-piperazine the 2-(4-methyl-piperazino)-4-phenyl-6-chloro-3,4-dihydro-quinazoline is obtained, melting at 163–164° after recrystallization from ethanol.

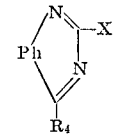
What is claimed is:

1. The process for the preparation of compounds having the formula



in which Ph is a member selected from the group consisting of 1,2-phenylene, (lower alkyl)-1,2 - phenylene, (lower alkoxy)-1,2-phenylene, (lower alkylmercapto)-1, 2-phenylene, (halogeno) - 1,2 - phenylene, (trifluoromethyl)-1,2-phenylene and (nitro)-1,2-phenylene, R_4 is a member selected from the group consisting of phenyl, (lower alkyl)-phenyl, (lower alkoxy)-phenyl, (lower alkylmercapto) - phenyl, (halogeno) - phenyl, (trifluoromethyl)-phenyl, (nitro)-phenyl, pyridyl, (lower alkyl)-pyridyl, thienyl and (lower alkyl)-thienyl, and X is a member selected from the group consisting of hydroxy,

mercapto, chloro or bromo, each of said lower alkyl, lower alkoxy and lower alkylmercapto moieties having 1 to 4 carbon atoms, which consists in reducing a compound having the formula



with a member selected from the group consisting of an alkali metal borohydride and an alkaline earth metal borohydride.

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U.S. Cl. X.R.

260—247.5, 256.4, 256.5