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DERIVATIVES OF 4-N-(2-N,N-DIMETHYLAMINO-LOWER ALKYL)-AMINO QUINAZOLINE

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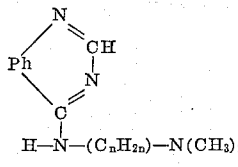
This is a continuation-in-part application of my application Serial No. 292,136, filed July 1, 1963, which in turn is a continuation-in-part application of my application Serial No. 282,243, filed May 22, 1963, and now abandoned, which in turn is a continuation-in-part application of my application Serial No. 274,818, filed April 22, 1963, and now abandoned.

The present invention concerns 2-unsubstituted 4-N-(2-N,N-dimethylamino-lower alkyl)-amino-quinazoline compounds and salts thereof. More especially, it relates to compounds of the formula:



in which Ph is a 1,2-phenylene (o-phenylene) radical, and the group of the formula $-(C_nH_{2n})-$ is lower alkylene separting the two nitrogen atoms by two carbon atoms, and the salts thereof. Also included within the scope of this invention is a process for the preparation of these compounds.

The 1,2-phenylene (o-phenylene) radical Ph, representing the hexacyclic carbocyclic aryl portion of the quinazoline ring system, is preferably unsubstituted, but may be substituted by one or more than one of the same or of different substituents attached to any of the four positions available for substitution. Substituents are, for example, lower alkyl, e.g. methyl, ethyl, n-propyl, isopropyl and the like, etherified hydroxyl, particularly lower alkoxy, e.g. methoxy, ethoxy, n-propyloxy, isopropyloxy, n-butyloxy and the like, esterified hydroxyl, especially halogeno (representing hydroxyl esterified by a hydrohalic acid), e.g. fluoro, chloro, bromo and the like, halogeno-lower alkyl, e.g. trifluoromethyl and the like, or any other suitable substituent. The 1,2-phenylene group Ph in the above formula is primarily 1,2-phenylene, but may also be (lower alkyl)-1,2-phenylene, (etherified hydroxy)-1,2-phenylene, such as (lower alkoxy)-1,2-phenylene and the like, (esterified hydroxy)-1,2-phenylene, such as (halogeno)-1,2-phenylene and the like, (trifluoromethyl)-1,2-phenylene, or any other suitably substituted 1,2-phenylene group.

The lower alkyl radical, separating N,N-dimethylamino from amino by two carbon atoms and represented in the above formula by the group of the formula $-(C_nH_{2n})-$, stands for lower alkylene having from two to three carbon atoms (i.e. the letter *n* stands preferably for one of the integers 2 and 3) and separates N,N-dimethylamino from amino by two carbon atoms. Such alkylene group is preferably 1,2-ethylene, but may also be 1-methyl-1,2-ethylene or 2-methyl-1,2-ethylene.

Salts of the compounds of this invention are acid addition salts, such as pharmaceutical acceptable acid addition salts with inorganic acids, e.g. hydrochloric, hydrobromic, sulfuric, phosphoric acids and the like, or organic acids, such as organic carboxylic acids, e.g. acetic, propionic, pivalic, glycolic, lactic, malonic, succinic, maleic, hydroxymaleic, malic, tartaric, citric, benzoic, salicylic, 2-acetoxybenzoic, nicotinic, isonicotinic acid and

the like, or organic sulfonic acids, e.g. methane sulfonic, ethane sulfonic, ethane 1,2-disulfonic, 2-hydroxyethane sulfonic, p-toluene sulfonic, naphthalene 2-sulfonic acid and the like. Other acid addition salts may also be useful as intermediates, for example, in the preparation of pharmaceutically acceptable acid addition salts, or may serve in the purification of the free compounds, as well as for identification or characterization purposes. Salts for the latter are, for example, those with acidic organic nitro compounds, e.g. picric, picrolonic, flavianic acid and the like, or with metal complex acid, e.g. phosphotungstic, phosphomolybdic, chloroplatinic, Reinecke acid and the like. Mono- or poly-salts may be formed.

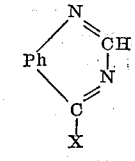
The compounds of this invention exhibit strong analgesic effects accompanied by a low degree of toxicity. They are, therefore, useful as annalgesic agents having an improved therapeutic ratio capable of raising the threshold of pain, and thus alleviate pain or the symptoms thereof, such as acute pains caused by surgery, accidents and the like, pain caused by spastic conditions, e.g. headaches and the like, or chronic pains connected with arthritic conditions and the like.

It is well-established that in pharmacological experiments, the potent analgesic effects of known morphine-type compounds with addicting properties are potentiated by amphetamine, and are accompanied by respiratory depression and depression of the spinal reflexes; furthermore, these effects are antagonized by N-allyl-N-desmethyl-morphine (nalorphine). It has now been found that the analgesic effects of the compounds of this invention are not potentiated by amphetamine, and are not accompanied by respiratory depression or depression of the spinal reflexes; furthermore, their effects are not antagonized by N-allyl-N-desmethyl-morphine. It appears, therefore, that the compounds of this invention are free from addicting properties at pharmacologically effective doses.

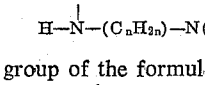
It has also been found that the free compounds of this invention are to a surprisingly high degree, water-soluble. They can, therefore, be used directly in case the compounds of this invention are to be used in an aqueous solution and do not have to be converted into a water-soluble salt; furthermore, the pressure of a solubilizer in such solution would not be required.

Particularly useful is the 4-N-(2-N,N-dimethylamino-ethyl)-amino-quinazoline, as well as the acid addition salts thereof, particularly its pharmaceutically acceptable acid addition salts; in addition to the above properties, this compound has an improved degree of toxicity, and is, therefore, of improved therapeutic ratio.

The compounds of this invention are prepared according to known methods, for example, by converting in a 2-unsubstituted 4-X-quinazoline compound, particularly in a compound of the formula:

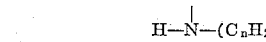


in which Ph has the previously-given meaning, and X is a group capable of being converted into an N-(2-N,N-dimethylamino-lower alkyl)-amino group, particularly into a group of the formula



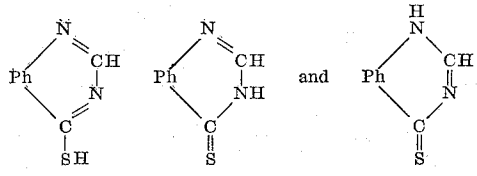
in which the group of the formula $-(C_nH_{2n})-$ has the previously-given meaning, or a tautomer thereof, or a salt of such compound, the group X into the N-(2-N,N-

dimethylamino-lower alkyl)-amino group, particularly into the group of the formula

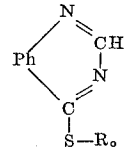


in which the group of the formula $-(C_nH_{2n})-$ has the previously-given meaning, and, if desired, converting a resulting salt into the free compound or into another salt; and/or, if desired, converting a resulting compound into a salt thereof, and/or, if desired, separating a resulting mixture of isomers into the single isomers.

In the starting material, a preferred substituent X, capable of being converted into the N-(2-N,N-dimethylamino-lower alkyl)-amino group, is a mercapto group, a thiono group or a substituted mercapto group. The preferred starting material is, therefore, a 2-unsubstituted 4-mercapto-quinazoline compound or a tautomer thereof, or a salt of such compound, particularly a compound having one of the tautomeric formulae:



in which formulae pH has the previously-given meaning, as well as a compound having the formula:



in which Ph has the previously-given meaning, and R_o is an organic radical, such as a lower aliphatic group, for example, lower alkyl, e.g. methyl, ethyl, isopropyl and the like, or any other suitable organic group, such as phenyl-lower alkyl, e.g. benzyl and the like, or a salt of such compound.

The conversion of the group X into the N-(2-N,N-dimethylamino-lower alkyl)-amino group is carried out by reacting the above 4-X-quinazoline starting material, in which X is a mercapto group, a thiono group, or a substituted mercapto group, with an N-(2-N,N-dimethylamino-lower alkyl)-amine or a salt thereof, particularly with a compound of the formula $H_2N-(C_nH_{2n})-N(CH_3)_2$, in which the group of the formula $-(C_nH_{2n})-$ has the previously-given meaning, or a salt thereof. The reaction is preformed according to known methods, preferably at an elevated temperature; if desired, an excess of the N-(2-N,N-dimethylamino-lower alkyl)-amine may be employed. The reaction may be carried out in the absence or in the presence of a diluent, e.g. ethanol and the like, or a mixture of solvents, if necessary, in a closed vessel, and/or in the atmosphere of an inert gas.

The starting materials used in the above modification of the process of this invention are known or are prepared according to known methods; preferably, they are obtained, for example, by reacting a 2-unsubstituted quinazolin-4-one compound or a tautomeric 4-hydroxy-quinazoline compound with a reagent capable of replacing oxo or hydroxyl by thiono or mercapto, such as phosphorus pentasulfide and the like, which is preferably used in the presence of a suitable diluent, e.g. xylene and the like, and at an elevated temperature. An unsubstituted mercapto group may be converted into a substituted mercapto group according to known methods, for example, by forming an alkali metal derivative of the 4-mercapto-quinazoline compound and reacting it with a reactive ester compound, such as a lower alkyl halide, a di-lower alkyl sulfate, a phenyl-lower alkyl halide and the like.

Another group representing X in the 4-X-quinazoline starting material is a reactive functionally converted hydroxyl group, especially a reactive etherified hydroxyl group or a reactive esterified hydroxyl group. A suitable etherified hydroxyl group is especially lower alkoxy, e.g. methoxy, ethoxy and the like, whereas a reactive esterified hydroxyl group is especially halogeno (representing hydroxyl esterified with a hydrohalic acid) having preferably an atomic weight greater than 19, e.g. chloro, bromo and the like, as well as any other hydroxyl group esterified with a strong inorganic or organic acid, such as a strong organic sulfonic acid, e.g. p-toluene sulfonic acid and the like.

The conversion of a reactive functionally converted hydroxyl group, particularly of lower alkoxy or halogeno, into the desired N-(2-N,N-dimethylamino-lower alkyl)-amino group is carried out according to the method described above, i.e. by treating the appropriate starting material with an N-(2-N,N-dimethylamino-lower alkyl)-amine, particularly with a compound of the formula $H_2N-(C_nH_{2n})-N(CH_3)_2$, in which the group of the formula $-(C_nH_{2n})-$ has the previously-given meaning, or a salt thereof. The reaction is carried out in the absence or in the presence of a diluent or a mixture of diluents, preferably at an elevated temperature, and, if necessary, in a closed vessel, and/or, in the atmosphere of an inert gas, e.g. nitrogen.

The above 2-unsubstituted 4-reactive functionally converted hydroxy-quinazoline starting materials are known or are prepared according to known methods. For example, the 2-unsubstituted 4-halogeno-quinazoline starting materials are obtained from the corresponding quinazoline-4-one compounds or tautomeric 4-hydroxy-quinazoline compounds by treating such compounds with a suitable halogenating reagent capable of replacing an oxo group or a hydroxyl group by halogeno, for example, with a phosphorus halide, e.g. phosphorus pentachloride, phosphorus tribromide and the like, or a thionyl halide, e.g. thionyl chloride and the like, preferably at an elevated temperature, and, if necessary, in the presence of a suitable diluent. Other 4-reactive esterified hydroxy-quinazoline starting materials are prepared according to known esterification procedures. 2 - unsubstituted 4-reactive etherified hydroxy-quinazoline starting materials, in which the reactive etherified hydroxyl group is especially lower alkoxy, are prepared, for example, by reacting a 2-unsubstituted 4-halogeno-quinazoline compound with a metal alcoholate, especially an alkali metal lower alkoxide, e.g. sodium or potassium methoxide, ethoxide, isopropoxide or n-butoxide and the like, preferably in the presence of the corresponding alcohol, especially lower alkanol, and at an elevated temperature, if necessary, in a closed vessel, and/or in the atmosphere of an inert gas.

Another group X is a 4-X-quinazoline starting material, capable of being converted into the desired N-(2-N,N-dimethylamino-lower alkyl)-amino group, is the cyano group as represented by the formula

Conversion of such group into N-(2-N,N-dimethylamino-lower alkyl)-amino is carried out as described above, for example, by reacting a 2-unsubstituted 4-cyano-quinazoline compound with the appropriate N-(2-N,N-dimethylamino-lower alkyl)-amine, preferably in the presence of a diluent, such as a lower alkanol, e.g methanol and the like, if necessary, at an elevated temperature, and/or in a closed vessel.

The starting materials used in the above modification of the procedure of this invention are known or may be prepared according to known methods, for example, by reacting a 2,4-unsubstituted quinazoline compound with a saturated solution of hydrogen cyanide in methanol in a sealed tube.

Another group X in a 4-X-quinazoline starting material, capable of being converted into the desired N-(2-N,

N-dimethylamino-lower alkyl)-amino group, is amino as represented by the formula

$$-\overset{|}{N}H_2$$

Conversion of such group into N-(2-N,N-dimethylamino-lower alkyl)-amino is carried out according to known methods; for example, a 2-unsubstituted 4-amino-quinazoline compound or a salt thereof, may be treated with a reactive ester of a 2-N,N-dimethylamino-lower alkanol, particularly with a compound of the formula

$$X_o—(C_nH_{2n})—N(CH_3)_2$$

in which the group of the formula $—(C_nH_{2n})—$, separating N,N-dimethylamino from X_o by two carbon atoms, has the previously-given meaning, and X_o is a reactive esterified hydroxyl group, or a salt of such compound. The reactive esterified hydroxyl group represented by X_o is particularly halogeno (i.e. hydroxyl esterified by a hydrohalic acid), having an atomic weight greater than 19, e.g. chloro, bromo and the like, as well as an organic sulfonyloxy group, e.g. 4-methyl-phenyl-sulfonyloxy and the like, or any analogous reactive esterified hydroxyl group. The above reaction is carried out according to known methods; preferably, it is performed at an elevated temperature, and, if necessary, in the presence of a diluent, and/or of a salt-forming reagent, such as an alkali metal hydride or an alkali metal amide, or any other corresponding reagent, and/or, of a base (which may also be furnished by an excess of the basic 4-amino-quinazoline starting material) to neutralize any generated acid or to liberate the basic reagent from any acid addition salt, and/or in a closed vessel, and/or in the atmosphere of an inert gas, e.g. nitrogen.

The starting materials used in the above modification of the process of this invention are known or may be prepared according to known methods, for example, by converting in a 2-unsubstituted 4-X-quinazoline compound, in which X is mercapto or halogeno, the group X into the amino group, for example, by treatment with ammonia or an ammonia-furnishing reagent.

The group X in the above 4-X-quinazoline starting material may also represent an N-(2-N,N-dimethylamino-lower alkanoyl)-amino group or an N-(2-N,N-dimethylamino-lower thioalkanoyl)-amino group, particularly the group of the formula

$$H—\overset{|}{N}—(CY—C_{n-1}H_{2n-2})—N(CH_3)_2$$

in which Y stands for oxo of the formula =O or thiono of the formula =S, and in which the portion of the formula $—CY—C_{n-1}H_{2n-2}—$ separates N,N-dimethylamino from amino by two carbon atoms. 2-unsubstituted 4-N-(2-N,N-dimethylamino-lower alkanoyl)-amino-quinazoline starting materials and 2-unsubstituted 4-N-(2-N,N-dimethylamino-lower thioalkanoyl)-amino-quinazoline starting materials are converted into the desired compounds of this invention according to known methods capable of replacing oxo in a carbonyl group or thiono in a thiocarbonyl group by two hydrogen atoms.

Replacement of oxo by two hydrogen atoms is carried out by reduction and is preferably achieved by treating the appropriate starting material with an aluminum hydride, particularly an alkali metal aluminum hydride, e.g. lithium aluminum hydride, sodium aluminum hydride and the like, or an alkaline earth metal aluminum hydride, e.g. magnesium aluminum hydride and the like, or aluminum hydride. If necessary, activators, such as, for example, aluminum chloride, may be used together with the hydride reducing reagent. The reduction with these reagents is preferably performed in the presence of an inert solvent, particularly an ether, such as a di-lower alkyl ether, e.g. diethyl ether, dipropyl ether and the like, a cyclic ether, e.g. tetrahydrofuran, p-dioxane and the like, or any other suitable solvent, and preferably at an elevated temperature. Conversion of the carbonyl portion of an amide grouping may also be achieved by treating the appropriate starting material with hydrogen in the presence of certain catalysts, such as a copper-chromium catalyst and the like, by electrolytic reduction or any other suitable method.

Replacement of sulfur in a thiocarbonyl group by two hydrogens may be carried out by desulfurization according to known methods, for example, by treatment with a freshly prepared hydrogenation catalyst, such as Raney nickel, in an alcoholic solvent, e.g. methanol, ethanol and the like, if desired, in the presence of hydrogen, by electrolytic reduction and the like.

The starting materials used in the above modification of the procedure of this invention are prepared, for example, by reacting a 2-unsubstituted 4-amino-quinazoline compound with a 2-N,N-dimethylamino-lower alkanoic acid halide, e.g. chloride, bromide and the like; this reaction may be carried out in the presence of a liquid organic base, e.g. pyridine and the like, which may also serve as the diluent, and/or of an inert solvent, e.g. benzene, toluene and the like, if necessary, by using an excess of the basic starting material or an additional base, e.g. potassium carbonate and the like, to neutralize any generated acid.

In a resulting 4-N-(2-N,N-dimethylamino-lower alkanoyl)-amino-quinazoline starting material, the carbonyl portion of the amide grouping can be replaced by thiocarbonyl, for example, by treatment with a reagent capable of replacing oxo by thiono, e.g. phosphorus pentasulfide and the like, as previously described.

The group X in a 4-X-quinazoline starting material may also represent an N-(2 N,N-dimethylamino-2-oxo-lower alkyl)-amino group or an N-(2-N,N-dimethylamino-2-thiono-lower alkyl)-amino group, particularly a group of the formula

$$H—\overset{|}{N}—(C_{n-1}H_{2n-2}—CY)—N(CH_3)_2$$

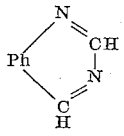
in which Y has the previously-given meaning, and the portion of the formula $—(C_{n-1}H_{2n-2}—CY)—$ separates N,N-dimethylamino from amino by two carbon atoms. In the 2-unsubstituted 4-N-(2-N,N-dimethylamino-2-oxo-lower alkyl)-amino-quinazoline starting materials and 2-unsubstituted 4-N-(2-N,N-dimethylamino-2-thiono-lower alkyl)-amino-quinazoline starting materials, the oxo group or the thiono group are replaced by two hydrogens according to known methods, such as those previously described.

The starting materials used in the above modification of the process for the manufacture of the compounds of this invention are prepared according to known methods. For example, a 2-unsubstituted 4-amino-quinazoline compound may be reacted with a 2-(reactive esterified hydroxy)-lower alkanoic N,N-dimethylamide, particularly a compound of the formula $X_o—(C_{n-1}H_{2n-2}—CO)—N(CH_3)_2$, in which X_o has the previously-given meaning (being particularly halogeno having an atomic weight greater than 19, e.g. chloro, bromo and the like) and substitutes the α-carbon atom, and the portion of the formula $—(C_{n-1}H_{2n-2}—CO)—$ separates N,N-dimethylamino from the reactive esterified hydroxyl group X_o by two carbon atoms. The reaction of the 2-unsubstituted 4-amino-quinazoline intermediate with the 2-(reactive esterified hydroxy)-lower alkanoic N,N-dimethylamide is carried out in the presence of an appropriate diluent, for example, a liquid organic base, e.g. pyridine and the like, to neutralize any generated acid, and, if necessary, at an elevated temperature.

In a resulting 4-N-(2-N,N-dimethylamino-2-oxo-lower alkyl)-amino-quinazoline starting material, the oxo group may be replaced by thiono, for example, by treating it with a suitable reagent, e.g. phosphorus pentasulfide and the like, as previously described.

The compounds of this invention are also prepared by

reacting a 2-unsubstituted quinazoline compound, particularly a compound of the formula:

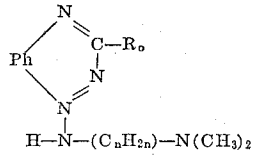


in which Ph has the previously-given meaning, or a salt thereof with an N-(2-N,N-dimethylamino-lower alkyl)-amine, especially a compound of the formula $H_2N-(C_nH_{2n})-N(CH_3)_2$, in which the group of the formula $-(C_nH_{2n})-$ has the previously-given meaning, and, if necessary, converting any resulting 2-unsubstituted 4-N-(2-N,N-dimethylamino-lower alkyl)-amino-3,4-dihydro-quinazoline compound into the desired 2-unsubstituted 4-N-(2-N,N-dimethylamino-lower alkyl)-amino-quinazoline compound by oxidation, and, if desired, carrying out the optional steps.

The above reaction is carried out according to known methods, preferably in the presence of a suitable salt-forming reagent, such as an alkali metal hydride and the like, and in the presence of an appropriate diluent, e.g. N,N-dimethyl-aniline and the like. Usually it is performed at an elevated temperature, and if necessary, in a closed vessel, and/or in the atmosphere of an inert gas.

If necessary a resulting 4-N-(2-N,N-dimethylamino-lower alkyl)-amino-3,4-dihydro-quinazoline compound is converted into the desired 4-N-(2-N,N-dimethylamino-lower alkyl)-amino-quinazoline by oxidation. The latter is performed according to known methods, for example, by air oxidation, or by treatment with any other suitable oxidation reagent, such as potassium ferric cyanide, iodine and the like, preferably in the presence of a diluent.

The compounds of this invention are also prepared by replacing in a 4-N-(2-N,N-dimethylamino-lower alkyl)-amino-2-R_o-quinazoline, particularly in a compound of the formula:



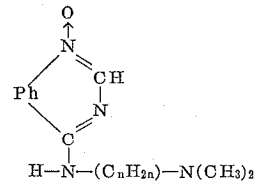
in which Ph and the group of the formula-(C_nH_{2n})-have the previously-given meaning, and R_o is a substituent capable of being replaced by hydrogen, or a salt thereof, the group R_o by hydrogen, and, if desired, carrying out the optional steps.

A group R_o capable of being replaced by hydrogen is especially a reactive functionally converted hydroxyl group, such as a reactive esterified hydroxyl group, particularly halogeno, e.g. chloro, bromo and the like, or any other suitable group capable of being replaced by hydrogen. The group R_o is removed according to known methods, usually by reduction, e.g. treatment with hydrogen in the presence of a suitable catalyst, such as a palladium catalyst and the like, if necessary under increased pressure, and/or at an elevated temperature, or any other equivalent reducing method.

The starting material is prepared according to known procedures, usually by converting in a 2-R_o-4-X-quinazoline, in which R_o and X have the previously-given meaning, the group X into the N-(2-N,N-dimethylamino-lower alkyl)-amino group according to any of the previously-described procedures.

The compounds of this invention are also prepared, for example, by eliminating in a 2-unsubstituted 4-N-(2-

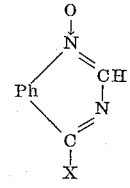
N,N-dimethylamino-lower alkyl)-amino-quinazoline N-oxide, particularly in a compound of the formula:



in which Ph and the group of the formula $-(C_nH_{2n})-$ have the previously-given meaning, or a salt thereof, the N-oxide grouping, and, if desired, carrying out the optional steps.

Removal of the N-oxide grouping is carried out according to known methods, usually by treatment with hydrogen activated by a metal catalyst, e.g. a nickel catalyst and the like, or any other procedure, such as reacting the starting material with a phosphorus halide, e.g. phosphorus trichloride and the like.

The starting materials used in the above procedure, especially those having the above formula, and particularly the 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline-1-oxide, as well as the acid addition salts thereof, are new. Apart from serving as starting materials, they also show analgesic effects and are intended to be included within the scope of this invention. They are prepared according to known methods, preferably by converting in a 2-unsubstituted 4-X-quinazoline N-oxide, especially a compound of the formula:



in which Ph and X have the previously-given meaning or a salt thereof, the group X into the N-(2-N,N-dimethylamino-lower alkyl)-amino group, especially into the group of the formula $H-N-(C_nH_{2n})-N(CH_3)_2$, in which the group of the formula $-(C_nH_{2n})-$ has the previously-given meaning, and, if desired, carrying out the optional steps. The conversion of the group X, which is above all a reactive functionally converted hydroxyl group, especially a reactive etherified hydroxyl group, such as lower alkoxy, into desired N-(2-N,N-dimethylamino-lower alkyl)-amino group is carried out as previously described.

A resulting acid addition salt of a compound prepared according to the process of this invention may be converted into the free compound, for example, by reacting it with an alkaline reagent, such as a metal hydroxide, e.g. lithium hydroxide, sodium hydroxide, potassium hydroxide, calcium hydroxide and the like, a metal carbonate, e.g. sodium, potassium or calcium carbonate or hydrogen carbonate and the like, ammonia and the like, or by treatment with a suitable hydroxyl ion exchange resin.

A resulting acid addition salt of a compound prepared according to the process of this invention may also be converted into another salt; for example, a salt with an inorganic acid may be reacted with a suitable metal, e.g. sodium, silver, barium and the like, salt of an acid, in the presence of a diluent, in which a resulting inorganic compound is insoluble and is thus removed from the reaction. Conversion of an acid addition salt into another acid addition salt may also be achieved by treatment with an anion exchange preparation.

A free compound resulting from the process of this invention may be converted into an acid addition salt thereof by reacting it or a solution thereof in a suitable solvent or solvent mixture with an acid or a solution thereof, or with an anion exchange preparation, and

isolating the desired salt. A salt may be obtained in the form of a hydrate thereof or may include solvent of crystallization.

A mixture of resulting isomeric compounds may be separated into the single isomers. For example, racemates may be resolved into the optically active d- and l-forms according to known resolution procedures, for example, by forming a salt of the free racemic compound with one of the optically active forms of an acid containing an asymmetric carbon atom. Especially useful as optically active forms of salt-forming acids having an asymmetric carbon atom are D-tartaric (l-tartaric) acid and L-tartaric (d-tartaric) acid, as well as the optically active forms of malic, mandelic, 10-camphor sulfonic, quinic acid and the like. A resulting mixture of salts is separated on the basis of physico-chemical differences, for example, by fractional crystallization; a separated salt may then be converted into the free and optically active compound as described above, and a free and optically active base may be converted into its acid addition salt according to the procedures described above.

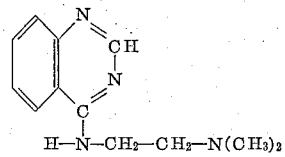
The invention also comprises any modification of the process, wherein a compound formed as an intermediate at any stage of the process is used as starting material and the remaining step(s) of the process is(are) carried out, as well as any new intermediates.

In the process of this invention such starting materials are preferably used which lead to final products mentioned in the beginning as preferred embodiments of the invention.

The following examples are intended to illustrate the invention and are not to be construed as being limitations thereon. Temperatures are given in degrees centigrade.

Example 1

To a solution of 0.95 g. of 4-mercapto-quinazoline (or its tautomer 3H-quinazolin-4-thione) in 10 ml. of N,N-dimethylethylenediamine is added 10 ml. of ethanol. The solution is refluxed for four hours and is then evaporated to dryness under reduced pressure. The solid residue (yield: 0.70 g.) is crystallized from a mixture of acetone and hexane to yield the desired 4-N-(2-N,N-dimethyl-aminoethyl)-amino-quinazoline of the formula:



which upon further recrystallizations from cyclohexane melts at 146–148°.

The starting material used in the above procedure is prepared according to the method described by Leonard et al., J. Org. Chem., vol. 11, p. 349 (1946): A mixture of 7.3 g. of 4-hydroxy-quinazoline (or its tautomer 3H-quinazolin-4-one) and 11.1 g. of phosphorus pentasulfide in 500 ml. of xylene is refluxed for two hours while stirring. After cooling, the reaction mixture is extracted with 100 ml. of 2 N aqueous sodium hydroxide; the aqueous phase is filtered and neutralized with glacial acetic acid. The resulting precipitate is filtered off and washed with water; the desired 4-mercapto-quinazoline is purified by recrystallization from N,N-dimethylformamide and melts above 300° after washing it with diethyl ether; yield: 4.2 g.

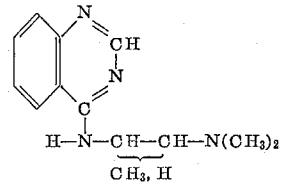
Example 2

To a diethyl ether solution of 4-N-(2-N,N-dimethyl-aminoethyl)-amino-quinazoline is added a solution of an equivalent amount of maleic acid in methanol; the resulting 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline maleate melts at 186–188° (with decomposition) after several recrystallizations from a mixture of methanol and diethyl ether.

Upon treating a solution of 4-N-(2-N,N-dimethyl-aminoethyl)-amino-quinazoline in ethanol with picric acid, the 4-N-(2-N,N-diethylamino-ethyl)-amino-quinazoline picrate is formed.

Example 3

A solution of 0.5 g. of 4-mercapto-quinazoline in 2.5 ml. of N,N-dimethylamino-isopropylamine and 2.5 ml. of ethanol is refluxed for four hours. The solvents are evaporated under reduced pressure, and the residue is diluted with pentane. Upon cooling, the desired 4-N-(N,N-dimethylamino-isopropyl)-aminoquinazoline of the formula:



solidifies and is recrystallized several times from pentane, M.P. 99–101°.

The N,N-dimethylamino-isopropylamine used as the reagent is prepared as follows: A mixture of 31.6 g. of N,N-dimethylaminoisopropyl chloride hydrochloride and 20.0 g. of potassium hydrogen carbonate in 200 ml. of toluene is heated until the evolution of carbon dioxide gas decreases. The solid material is filtered off; the filtrate is treated with 37.0 g. of potassium phthalimide, and the reaction mixture is refluxed for sixteen hours. After cooling and filtering, the filtrate is evaporated to dryness; the resulting oily residue solidifies upon adding pentane and cooling to yield 28.0 g. of N-(N,N-dimethylamino-isopropyl)-phthalimide, which melts at 57–59° after recrystallization from pentane.

A mixture of 20.0 g. of N-(N,N-dimethylamino-isopropyl)-phthalimide in 100 ml. of 20 percent hydrochloric acid is refluxed for three hours and allowed to stand for several days. The solid material is filtered off and washed with water; the combined filtrates are concentrated to a small volume and made strongly basic with an aqueous solution of sodium hydroxide. The resulting oil is extracted with methylene chloride, the organic solution is dried over sodium sulfate and evaporated to dryness. The desired N,N-dimethylamino-isopropyl-amine is purified by distilling the residue and is collected at about 50°/15 mm.

Example 4

A solution of 2.3 g. of 4-N-(N,N-dimethyl-carbamyl-methyl)-amino-quinazoline in 30 ml. of tetrahydrofuran is added dropwise over a period of thirty minutes to a suspension of 0.38 g. of lithium aluminum hydride in 50 ml. of tetrahydrofuran while cooling in an ice-bath and maintaining vigorous stirring. The reaction mixture is then refluxed for six hours; the resulting complex is destroyed by adding a small excess of water in tetrahydrofuran. The mixture is filtered, the filtrate is evaporated to dryness, and the resulting oil crystallizes on adding cyclohexane to yield the crude 4-N-(2-N,N-dimethyl-amino-ethyl)-amino-quinazoline, which, upon further recrystallization from cyclohexane, melts at 146–148°.

The starting material used in the above procedure is prepared as follows: A mixture of 1.0 g. of 4-amino-quinazoline (prepared according to the method described by Morley et al., J. Chem. Soc., p. 1354 (1949)) and 0.16 g. of sodium hydride in 50 ml. of toluene is refluxed for two hours. A solution of 0.83 g. of α-chloro-N,N-dimethylacetamide in 10 ml. of toluene is added dropwise over a period of fifteen minutes while stirring. The reaction mixture is refluxed for another hour and is then evaporated to dryness under reduced pressure. Water is added to the residue; the crude solid 4-N(N,N-dimethyl-carbamyl-methyl)-amino-quinazoline is collected, dried on the filter and used without further purification.

Example 5

A mixture of 1.0 g. of 4-cyano-quinazoline and 1.0 g. of N,N-dimethyl-1,2-ethylenediamine is allowed to stand at room temperature for one hour, and is then warmed on the steam bath for fifteen minutes. The excess of N,N-dimethyl-1,2-ethylene diamine is evaporated under reduced pressure, and the residue is extracted with boiling cyclohexane. The organic extract is concentrated and allowed to stand while cooling to yield the desired 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline, which is identical with the compound obtained according to the procedure described in Example 1.

The starting material used in the previous procedure is prepared as follows: A solution of 1.0 g. of quinazoline in 30 ml. of methanol is cooled to 0° and is treated for 1½ hours with an excess of hydrogen cyanide. The solvent is then removed to yield the 4-cyano-3,4-dihydroquinazoline, M.P 128–129°. To a mixture of 0.5 g. of the latter in a solution of 0.66 g. of potassium hydroxide in 2 ml. of water and 10 ml. of benzene is added 2.65 g. of potassium ferricyanide in 13 ml. of water over a period of one hour. The organic layer is separated to yield 0.2 g. of 4-cyano-quinazoline, whereas the aqueous phase yields another 0.18 g. of the same compound.

Example 6

A mixture of 1.0 g. of 4-chloro-quinazoline and 15 ml. of N,N-dimethyl-1,2-ethylenediamine is refluxed for three hours; the excess of N-N-dimethyl-1-2-ethylenediamine is removed under reduced pressure, and the residue is extracted with boiling cyclohexane. The organic extract yields 0.5 g. of the desired 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline which is identical with the compound formed according to the procedure described in Example 1.

The starting material used in the above procedure is described by Gabriel et al., Chem. Ber., vol. 29, p. 1300 (1896).

Example 7

A mixture of 1.0 g. of 4-amino-quinazoline and 0.2 g. of sodium hydride in 50 ml. of dry toluene is refluxed for two hours, and is then treated with a solution of 1.0 g. of 2-N,N-diethylamino-ethyl chloride (liberated from its hydrochloride with a cold, concentrated aqueous solution of sodium hydroxide in water) in 50 ml. of toluene, which is added dropwise over a period of fifteen minutes while stirring and cooling in an ice bath. The reaction mixture is allowed to warm to room temperature and is then heated on the steam bath for thirty minutes. After evaporating the solvent under reduced pressure, the residue is extracted with boiling cyclohexane; the desired 4-N-(2-N,N-dimethylaminoethyl) - amino - quinazoline is obtained by concentrating and cooling the organic extract.

The starting material used in the above procedure is prepared according to the method described by Morley et al., J. Chem. Soc., p. 1354 (1949).

Example 8

A mixture of 4.0 g. of N,N-dimethyl-1,2-ethylenediamine, 1.0 g. of sodium hydride and 20 ml. of N,N-dimethylaniline is heated at 145–150° for two hours. Over a period of fifteen minutes and while maintaining that temperature, a total of 1.0 g. of quinazoline is added, and heating is continued for an additional two hours. After standing overnight, the reaction product is decomposed with a minimum amount of water; the aqueous phase is extracted with diethyl ether, and the organic extract is dried over anhydrous sodium sulfate and concentrated. The residue is taken up into boiling cyclohexane; the solution is concentrated and chilled to yield the dried 4-N - (2-N,N-dimethylaminoethyl) - amino - quinazoline, which is identical with the product obtained from the procedure described in Example 1.

Example 9

A mixture of 1.0 g. of 4-methoxy-quinazoline, 10 ml. of N,N-dimethyl-1,2-ethylenediamine and 10 ml. of methanol is heated in a sealed tube at 150° for sixteen hours. The reaction product is then evaporated to dryness under reduced pressure and the residue is extracted with boiling cyclohexane. The organic extract is decolorized with a charcoal preparation, concentrated and chilled to yield the desired 4-N - (2 - N,N - dimethylaminoethyl) - amino-quinazoline.

The starting material is prepared according to the procedure described by Breukink et al., Rec. Trav. Chim., vol. 76, p. 401 (1957).

Example 10

A solution of 2.0 g. of 2-chloro-4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline in 100 ml. of warm methanol is shaken with hydrogen in the presence of 6.0 g. of palladium-on-charcoal. The reduction is complete after two hours; the catalyst is filtered off, the filtrate is evaporated and the residue is treated with aqueous sodium hydroxide. The aqueous phase is extracted with diethyl ether; the organic extract is dried over anhydrous sodium sulfate, and concentrated under reduced pressure. The desired 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline is obtained by extracting the residue with cyclohexane, concentrating the solution and cooling it.

The starting material used in the above procedure is prepared as follows: A mixture of 2.0 g. of 2,4-dichloroquinazoline (prepared according to the method described by Curd et al., J. Chem Soc., p. 775 (1947)), 20 ml. of water and 0.88 g. of N,N-dimethyl-1,2-ethylenediamine is stirred at room temperature. After one hour, the reaction mixture is made alkaline to Clayton yellow with 10 N aqueous sodium hydroxide solution. In order to maintain the alkalinity, the reaction mixture is treated at intervals with further amounts of sodium hydroxide until approximately the equivalent of 0.4 g. of sodium hydroxide has been added (about six hours). The reaction mixture is then acidified to Congo red with hydrochloric acid and filtered; the filtrate is treated with an excess of aqueous sodium hydroxide to precipitate a gummy material. The liquid phase is decanted, and the residue is triturated with diethyl ether. The desired 2-chloro-4-N-(2-N,N-dimethylaminoethyl)-amino - quinazoline is collected, washed with water, dried at room temperature and used without further purification.

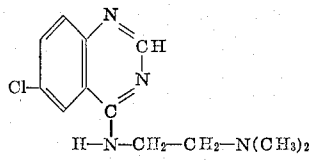
Example 11

To a solution of 1.0 g. of 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline-1-oxide in 20 ml. of methanol is added the Raney nickel catalyst, prepared from 1.5 g. of a 1:1-nickel:aluminum alloy and a 30 percent aqueous solution of sodium hydroxide, and the mixture is shaken under hydrogen at atmospheric pressure. After the absorption of the theoretical amount of hydrogen, the reaction is interrupted, the catalyst is filtered off and the filtrate is evaporated to dryness. The residue is crystallized from cyclohexane and yields the desired 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline, which is identical with the compound prepared according to the procedure described in Example 1.

The starting materials used in the above procedure is prepared as follows: A mixture of 1.0 g. of 4-methoxyquinazoline-1-oxide (prepared according to the method described by Yamanaka, Chem. Pharm. Bull. (Tokyo), vol. 7, p. 152 (1959)) and 10 ml. of N,N-dimethyl-1,2-ethylenediamine is placed in a sealed tube and heated at 100° for two hours. The reaction mixture is then evaporated to dryness under reduced pressure and the residue is crystallized from a mixture of diethyl ether and pentane to yield the 4-N-(2 - N,N - dimethylaminoethyl) - amino-quinazoline-1-oxide.

Example 12

A mixture of 2.5 g. of 6-chloro-4-mercapto-quinazoline (or its tautomer 6-chloro-3H-quinazolin-4-thione) and 15 ml. of N,N-dimethyl-1,2-ethylenediamine in 15 ml. of ethanol is refluxed for four hours. After evaporating the reaction mixture to dryness under reduced pressure, the solid residue is crystallized from diethyl ether to yield the 6-chloro-4-N-(2-N,N - dimethylamino)-amino-quinazoline of the formula:

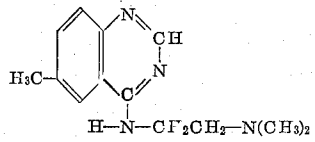


which melts at 169–171°.

The starting material used in the above procedure is prepared as follows: To a suspension of 23.0 g. of 6-chloro-4-hydroxy-quinazoline (prepared according to the procedure described by Magidson et al., J. Gen. Chem., vol. 8, p. 1797 (1938); C.A., vol. 33, p. 4993 (1939)) in 250 ml. of pyridine is added 32.0 g. of phosphorus pentasulfide. The exothermic reaction is maintained by refluxing for three hours; after cooling to a lower temperature, the reaction mixture is poured into about 500 ml. of water. The yellow-brown solid is filtered off, dried and then dissolved in about 200 ml. of a ten percent solution of sodium hydroxide in water. The solution is filtered, the filtrate is neutralized with hydrochloric acid (a 1:10-mixture of concentrated hydrochloric acid and water), and the yellow solid material is filtered off and dried at room temperature. The desired 6-chloro-4-mercaptoquinazoline melts over 300°; yield: 22.5 g.

Example 13

A mixture of 1.0 g. of 4-mercapto-6-methyl-quinazoline (or its tautomer 6-methyl-3H-quinazolin-4-thione) and 5 ml. of N,N-dimethyl-1,2-ethylenediamine in 5 ml. of ethanol is refluxed for four hours. The solid material is filtered off; the filtrate is evaporated, and the residue crystallizes upon cooling. The desired 4-N-(2-N,N-dimethylaminoethyl)-amino-6-methyl-quinazoline of the formula:



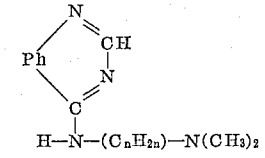
melts at 162–164° after recrystallization from ethyl acetate.

The starting material used in the above procedure is prepared as follows: A mixture of 5.0 g. of 5-methyl-anthranilic acid and 4.5 g. of formamide is heated to 140–150° for one hour. Upon cooling, the reaction product solidifies and is triturated three times with acetone to yield 4.6 g. of 6-methyl-quinazolin-4-one; the latter melts at 264–266° after recrystallization from methanol.

To a solution of 1.0 g. of 6-methyl-quinazolin-4-one in 25 ml. of pyridine is added 1.25 g. of phosphorus pentasulfide; the mixture is refluxed for three hours and, after cooling, is poured into water. The solid material is filtered off and dissolved in a ten percent aqueous solution of sodium hydroxide. Upon neutralizing with dilute hydrochloric acid, the yellow 4-mercapto-6-methyl-quinazoline precipitates and is filtered off; it melts above 310°.

By substituting the 4-mercapto-7-methoxy-quinazoline, the 6,7-dimethoxy-4-mercapto-quinazoline, the 4-mercapto-7-trifluoromethyl-quinazoline or analogous 4-mercapto-quinazoline compounds for the 4-mercapto-6-methyl-quinazoline in the above procedure, and reacting them with N,N-dimethyl-1,2-ethylenediamine as described before, 4-N-(2-N,N-dimethylaminoethyl)-amino-7-methoxy-quinazoline, 6,7-dimethoxy-4-N-(2-N,N-dimethylamino-ethyl) - amino - quinazoline, 4-N-(2,N,N-dimethylamino-ethyl)-amino-7-trifluoromethyl-quinazoline or analogous 4 - N - (2 - N,N-dimethylaminoethyl)-amino-quinazoline compounds are prepared.

Also included within the scope of this invention are the novel pharmaceutical compositions comprising essentially a pharmacologically effective amount of a 2-unsubstituted 4-N-(2-N,N - dimethylamino-lower alkyl)-amino-quinazoline compound, such as a compound of the formula:



in which Ph and the group of the formula $—(C_nH_{2n})—$ have the previously-given meaning, or a pharmaceutically acceptable acid addition salt thereof, as the active analgesic ingredient, and a pharmaceutically acceptable carrier.

Preferred compositions for the relief of pain are those comprising essentially a pharmacologically effective amount of 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline or a pharmaceutically acceptable acid addition salt thereof, as the active analgesic ingredient, and a pharmaceutically acceptable carrier.

The analgesic compositions of this invention represent versatile tools in raising the threshold and suppressing the symptons of many types of pain. Thus, they can be used to counteract light pains (e.g. toothaches, headaches and the like), as well as severe pains (e.g. post-operative pains, pains in connection with fractures and the like), and chronic pains (e.g. pains caused by arthitic conditions and the like.) Light pains require correspondingly smaller doses of the active analgesic ingredient, whereas severe and chronic pains have to be treated with higher doses of the active compound. Advantages of the pharmacologically active ingredient of the compositions of this invention are the considerable lack of undesirable side-effects and, for all practical purposes, the absence of toxic properties.

The analgesic compositions of this invention are prepared according to methods accepted in the art of manufacturing of pharmaceutical compositions, essentially by combining the active ingredient with a pharmaceutically acceptable, organic or inorganic carrier in specified proportions. The compositions usually contain at most equal amounts of the active analgesic ingredient and the inert carrier. Preferably, they are made up to contain from about 1 percent to at most 50 percent, by weight, of the active analgesic ingredient in the composition. In compositions for oral use (e.g. tablets, capsules and the like), the percentage by weight is from about 5 percent to at most 50 percent of the active material. In compositions for injection (e.g. solutions and the like), the percentage by weight is from about 1 percent to about 20 percent of the active ingredient.

In preparing pharmaceutically acceptable dosage unit forms, any one of a wide variety of preparations may be manufactured, such as tablets, capsules, pills, suppositories, solutions, suspensions and the like. In addition to the pharmacologically active component, there may be present additional substances commonly employed in the pharmaceutical art of manufacturing dosage unit compositions. These may include excipients, binders, fillers, lubricants, stabilizers, wetting agents, emulsifiers, buffers, and/or other ingredients.

The tablet, capsule, dragee and the like, provide for the preferred oral form of administration. These forms may be compounded to have from about 0.01 g. to about

0.1 g., such as from about 0.02 g. to about 0.05 g., of a 2-unsubstituted 4-N-(2-N,N-dimethylamino-lower alkyl)-amino-quinazoline compound, such as one of the above formula, particularly of 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline, or a pharmaceutically acceptable acid addition salt thereof, such as those with one of the above-mentioned inorganic or organic acids, as the active analgesic ingredient, per single dosage unit.

The inert fillers, binders, lubricants and other carrier materials normally used for the manufacture of the orally applicable tablets, capsules, dragees and the like, are employed in formulating the latter; examples of these materials are starches, e.g. corn starch, wheat starch, rice starch and the like, sugars, e.g. lactose, glucose, sucrose and the like, stearic acid, or salts thereof, e.g. magnesium stearate, calcium stearate and the like, aluminum magnesium silicate preparations, talc, tragacanth, acacia, polyethylene glycol and the like. The quantities of these ingredients may vary widely and depend, for example, upon the characteristics and size of the desired, orally applicable form, the method of its manufacture and the like. Encapsulation may also be effected, using, if necessary, the same excipients as those employed for the preparation of tablets. As has been indicated above, the compounding is generally effected in the manner known in the art, usually by preparing a granulation suitable for compression. Any compatible colors, approved and certified under the provisions of the Federal Food, Drug and Cosmetic Law may be used for the purpose of identification and the like.

Solutions for parenteral administration have from about 0.01 g./ml. to about 0.2 g./ml., preferably from about 0.01 g./ml. to about 0.05 g./ml., of a 2-unsubstituted 4-N-(2-N,N,-dimethylamino-lower alkyl) - amino-quinazoline compound, such as one of the above formula, particularly of 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline, or a pharmaceutically acceptable acid addition salt thereof with one of the above-mentioned inorganic or organic acids, as the active analgesic ingredient.

Primary solvents for solutions of injection are water or water-miscible organic solvents, such as lower alkanols, e.g. ethanol and the like. Other ingredients, particularly stabilizers, such as, for example, anti-oxidants, e.g. thiourea, sodium sulfide, sodium metabisulfite, ascorbic acid, cysteine hydrochloride, sodium formaldehyde sulfoxylate and the like, mono-thioglycerol, thiosorbitol and the like, buffers or buffer combinations to maintain a pH of about 7, such as, for example, acetic acid, potassium phthalate and sodium hydroxide, potassium dihydrogen phosphate and di-sodium hydrogen phosphate, potassium dihydrogen phosphate and sodium hydroxide, acetic acid and sodium acetate and the like, salts for making isotonic solutions, e.g. sodium chloride and the like, are added to ensure stable solutions for injection.

In addition to the active analgesic compound and the pharmaceutically acceptable carrier, pharmaceutical compositions of this invention may contain other pharmacologically active substances. Such combination preparations are prepared according to procedures analogous to those used for known combination preparations. Pharmacologically active compounds used in combination with the active analgesic ingredient of the compositions of this invention are, for example, other analgesic, such as those of the antipyretic type, e.g. 2-acetoxy-benzoic acid, phenyl salicylate, cinchophen, acetophenetidine, aminopyrin, 4-isopropyl-3-methyl - 1,2 - diphenyl-pyrazolone and the like. Other pharmacologically active compounds present in compositions containing the above-described analgesic ingredient, are, for example, narcotics, such as those of the barbiturate-type, e.g. phenobarbital, diallyl barbituric acid and the like, or any other pharmacologically active compound, which is known to be suitable in combination compositions having primarily analgesic effects.

Example 14

Tablets, each containing 0.025 g. of 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline, are prepared as follows (for 10,000 tablets):

Ingredients:	Grams
4-N-(2 - N,N - dimethylaminoethyl) - amino-quinazoline	250.0
Lactose U.S.P.	1600.0
Polyethyleneglycol 6000	80.0
Talc	60.0
Magnesium stearate	10.0
Alcohol 3A, q.s.	

The 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline, the lactose, the talc and the magnesium stearate are mixed in a suitable mixer, sieved through a No. 40 screen, again mixed and granulated with a solution of the polyethyleneglycol 6000 in the 3A alcohol. The wet granules are passed through a screen, dried, again screened through a No. 20 screen and compressed into tablets, weighing 0.2 g. each, using $11/32$ inch standard concave punches.

Example 15

Tablets, each containing 0.025 g. of 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline maleate, are prepared as follows (for 20,000 tablets):

Ingredients:	Grams
4-N-(2 - N,N - dimethylaminoethyl) - amino-quinazoline maleate	500.0
Lactose U.S.P.	3200.0
Polyethyleneglycol 6000	160.0
Talc	120.0
Magnesium stearate	20.0
Alcohol 3A, q.s.	

The tablets are prepared as described in Example 14.

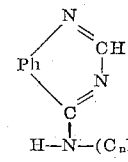
Example 16

Capsules, each containing 0.025 g. of 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline are prepared as follows (for 10,000 capsules):

Ingredients:	Grams
4-N-(2 - N,N - dimethylaminoethyl) - amino-quinazoline	250.0
Lactose U.S.P.	2210.0
Magnesium stearate	40.0

The ingredients are mixed in a suitable mixer, sieved through a No. 40 screen, and again mixed; 0.25 g. portions of the resulting mixture are then filled into No. 3 capsules.

Also included within the scope of this invention is a new method for the alleviation of pain, which comprises administering to a host requiring relief from pain, a pharmaceutical composition consisting essentially of a pharmacologically effective amount of a 2-unsubstituted 4-N-(2-N,N-dimethylamino-lower alkyl) - amino-quinazoline compound, such as a compound of the formula:



in which Ph and the group of the formula $—(C_nH_{2n})—$ have the previously-given meaning, or a pharmaceutically acceptable acid addition salt thereof, as the active analgesic ingredient, and a pharmaceutically acceptable carrier; compositions useful in the method of alleviating pain according to this invention are those described above.

A preferred method for the alleviation of pain comprises administering to a host requiring relief from pain a pharmaceutical composition consisting essentially of a pharmacologically effective amount of 4-N-(2-N,N-di-

methylaminoethyl)-amino-quinazoline or a pharmaceutically acceptable acid addition salt of such compound, as the active analgesic ingredient, and a pharmaceutically acceptable carrier; compositions useful in the method of alleviating pain according to this invention are those described above.

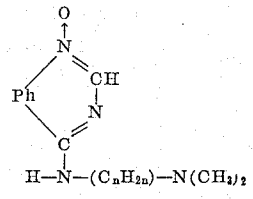
What is claimed is:

1. 4-N-(2-N,N-dimethylaminoethyl)-amino - quinazoline.

2. An acid addition salt of 4-N-(2-N,N-dimethylaminoethyl)-amino-quinazoline.

3. 4-N-(2-N,N-dimethylaminoethyl)-amino - quinazoline maleate.

4. A member selected from the group consisting of a compound of the formula:



in which Ph is 1,2-phenylene, and the group of the formula $-(C_nH_{2n})-$ is lower alkylene separating the two nitrogen atoms by two carbon atoms, and an acid addition salt thereof.

5. 4-N-(2-N,N-dimethylamino - lower alkyl) - amino-quinazoline-1-oxide.

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UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

Patent No. 3,301,855 January 31, 1967

Herbert Morton Blatter

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 13, line 9, for "dimethylamino)" read -- dimethylaminoethyl) --.

Signed and sealed this 28th day of November 1967.

(SEAL)
Attest:

Edward M. Fletcher, Jr.
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents