

PATENT SPECIFICATION

NO DRAWINGS

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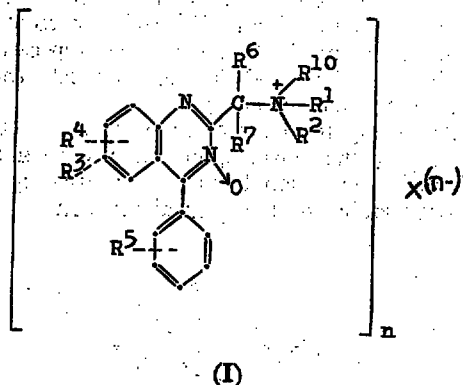
COMPLETE SPECIFICATION

Novel Quinazoline Derivatives and a Process for the Manufacture and Conversion thereof

We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with novel quinazoline derivatives and a process for the manufacture and conversion thereof.

The novel quinazoline derivatives provided by the invention may be formulated thus:



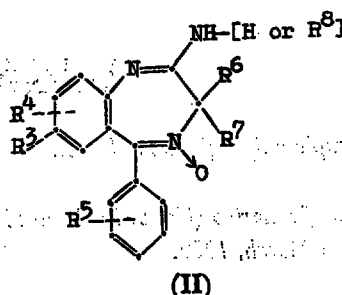
wherein R¹ and R² each represent a lower-alkyl group or together represent a lower-alkylene, aza-(lower alkylene), N-(lower alkyl) - aza - (lower alkylene), oxa - (lower alkylene) or thia - (lower alkylene) group, R³, R⁴ and R⁵ each represent a halogen atom or the trifluoromethyl, nitro or cyano group or a lower-alkyl or lower-alkoxy groups, R⁶ and R⁷ each represent a hydrogen atom or a

lower-alkyl group, R¹⁰ represents a lower-alkyl or aralkyl group, n is an integer and X⁽ⁿ⁻⁾ represents an anion of an acid having n displaceable hydrogen atoms and wherein the broken lines denote that the groups or atoms attached thereby are optional.

The novel derivatives aforesaid possess useful cardioactive or antibacterial properties. They may be used as medicaments in the form of pharmaceutical preparations which contain them in admixture with a compatible pharmaceutical carrier. This carrier, can be an organic or inorganic, solid or liquid carrier suitable for enteral (e.g. oral) or parenteral administration. For making up the preparations there may be employed inert substances such as water, gelatin, lactose, starches, magnesium stearate, talc, vegetable oils, gums, polyalkyleneglycols, petroleum jelly or any other compatible carrier useful for the preparation of medicaments. The pharmaceutical preparations may be in solid form (for example, as tablets, dragées, suppositories or capsules) or in liquid form (for example, as solutions, emulsions or suspensions). If desired, they may be sterilized and/or contain auxiliary substances such as preserving agents, stabilizing agents, wetting or emulsifying agents, salts for varying the osmotic pressure or buffers. They may also contain therapeutically useful substances other than the novel derivatives provided by the invention.

The novel derivatives aforesaid are also useful in that they can be converted in a manner to be described hereinafter into pharmaceutically useful benzodiaz[1,4]epine 4-oxides of the general formula

[Price 4s. 6d.]

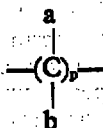


(II)

wherein R^3 , R^4 , R^5 , R^6 , R^7 and the broken lines have the significance given earlier and R^8 represents a lower-alkyl, lower-alkenyl, lower-alkynyl or (lower *cycloalkyl*)-(lower alkyl) group.

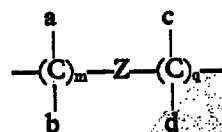
It will be appreciated that the term 'lower alkyl' is used in this description and in the claims appended hereto to mean a straight-chain or branched-chain alkyl group containing from one to seven carbon atoms such as methyl, ethyl, propyl, isopropyl and butyl.

The term 'lower alkenyl' is used to mean straight-chain and branched-chain alkenyl groups containing not more than seven carbon atoms (e.g. allyl, butenyl and isobutenyl) and the term 'lower alkynyl' is used to mean straight-chain and branched-chain alkynyl groups containing not more than seven carbon atoms (e.g. propynyl, butynyl and isobutynyl). The term 'lower alkoxy' is used to mean straight-chain and branched-chain alkoxy groups containing from one to seven carbon atoms and the term 'lower *cycloalkyl*' is used to mean a *cycloalkyl* group containing from three to six carbon atoms. R^1 and R^2 , when taken together, represent a lower-alkylene, aza-(lower alkylene), N-(lower alkyl)-aza-(lower alkylene), oxa-(lower alkylene) or thia-(lower alkylene) group such that together with the nitrogen atom to which they are attached they form a heterocyclic radical containing from three to seven ring atoms. The term 'lower alkylene' denotes a straight-chain or branched-chain alkylene group represented by the formula



wherein the symbols a and b each represent a hydrogen atom or a lower-alkyl group and can be the same or different and p is 2, 3, 4, 5 or 6.

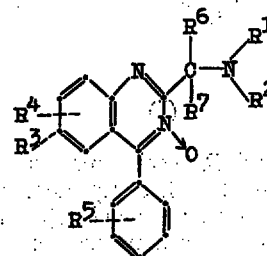
The terms 'aza-(lower alkylene)', 'N-(lower alkyl)-aza-(lower alkylene)', 'oxa-(lower alkylene)' and 'thia-(lower alkylene)' represent an alkylene chain which is interrupted by a single NH or N-(lower alkyl) group or an oxygen or sulphur atom and can be represented by the formula



wherein the symbols a , b , c and d each represent a hydrogen atom or a lower-alkyl group and can be the same or different, Z represents an oxygen or sulphur atom or an —NH— or —N-(lower alkyl)-grouping and m and y each represent 1, 2, 3 or 4 provided that the sum of m and y is not greater than 5. The term 'halogen' means iodine, bromine, chlorine and fluorine. Chlorine and fluorine are preferred. The aralkyl group is preferably a benzyl group. The anion represented by $X^{(n-)}$ is preferably a pharmaceutically acceptable anion.

Interesting classes of novel quinazoline derivatives provided by the invention comprise those in which R^4 and R^5 are absent and R^6 and R^7 each represent a hydrogen atom, those in which R^4 and R^5 are absent, R^6 and R^7 each represent a hydrogen atom and R^8 is present and represents a chlorine atom, those in which R^4 and R^5 are absent; R^6 and R^7 each represent a hydrogen atom, R^8 is present and represents a chlorine atom and R^1 and R^2 together represent an ethylene, propylene, butylene, pentamethylene or hexamethylene group and those in which R^4 and R^5 are absent, R^6 and R^7 each represent a hydrogen atom, R^8 is present and represents a chlorine atom and R^1 and R^2 together represent a 3-oxa-pentamethylene group. Other interesting quinazoline derivatives provided by the invention are those in which R^4 and R^5 are absent, R^6 and R^7 each represent a hydrogen atom, R^8 is present and represents a chlorine atom and R^1 , R^2 and R^{10} each represent a methyl group.

According to the process provided by the invention, the novel quinazoline derivatives aforesaid are manufactured by treating a tertiary amine of the general formula



(III)

wherein R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 and the broken lines have the significance given earlier, with a quaternizing agent and, if desired, exchanging the resulting quaternary salt anion with a different anion.

The tertiary amine starting materials of formula III are known and can be readily prepared by known procedures. Interesting classes of tertiary amine starting materials of formula II comprise those in which R⁴ and R⁵ are absent and R⁶ and R⁷ each represent a hydrogen atom, those in which R⁴ and R⁵ are absent, R⁶ and R⁷ each represent a hydrogen atom and R³ is present and represents a chlorine atom, those in which R⁴ and R⁵ are absent, R⁶ and R⁷ each represent a hydrogen atom, R³ is present and represents a chlorine atom and R¹ and R² together represent an ethylene, propylene, butylene, pentamethylene or hexamethylene group and those in which R⁴ and R⁵ are absent, R⁶ and R⁷ each represent a hydrogen atom, R³ is present and represents a chlorine atom and R¹ and R² together represent a 3 - oxa - pentamethylene group. 6 - Chloro - 4 - phenyl - 2 - dimethylaminomethyl - quinazoline 3 - oxide is an especially interesting tertiary amine starting material of formula III and the treatment thereof with a compound of formula IV in which R¹⁰ represents a methyl group constitutes an especially interesting embodiment of the present process. Specific examples of other tertiary amine starting materials of formula III are 2 - dimethylaminomethyl - 4 - phenyl - quinazoline 3 - oxide, 2 - hexamethyleniminomethyl - 4 - phenyl - quinazoline 3 - oxide, 2 - morpholinomethyl - 4 - phenyl - quinazoline 3 - oxide, 6 - chloro - 2 - [(1' - pyrrolidinyl) - methyl] - 4 - phenyl - quinazoline 3 - oxide, 6 - chloro - 4 - phenyl - 2 - piperidinomethyl - quinazoline 3 - oxide, 6 - chloro - 2 - ethyleniminomethyl - 4 - phenyl - quinazoline 3 - oxide, 6 - chloro - 2 - morpholinomethyl - 4 - phenyl - quinazoline 3 - oxide, 6 - chloro - 2 - [hexahydroazepinyl - (1) - methyl] - 4 - phenyl - quinazoline 3 - oxide, 6 - chloro - 2 - dimethylaminomethyl - 4 - phenyl - quinazoline 3 - oxide, 6 - trifluoromethyl - 2 - dimethylaminomethyl - 4 - phenyl - quinazoline 3 - oxide, 6 - chloro - 2 - dimethylaminomethyl - 4 - (2 - chloro - phenyl) - quinazoline 3 - oxide, 6 - chloro - 2 - dimethylaminomethyl - 4 - (2 - fluoro - phenyl) - quinazoline 3 - oxide, 6 - methyl - 4 - phenyl - 2 - piperidinomethyl - quinazoline 3 - oxide, 6 - chloro - 4 - phenyl - 2 - [(1' - piperazinyl) - methyl] - quinazoline 3 - oxide and 6 - chloro - 4 - phenyl - 2 - [(N⁴ - methyl - 1' - piperazinyl) - methyl] - quinazoline 3 - oxide.

The treatment (i.e. quaternization) of a tertiary amine of formula III with a quaternizing agent can be accomplished by any of the usual techniques for quaternizing amines. Thus, it can be accomplished using, as the quaternizing agent, a lower-alkyl halide (for example, methyl iodide, methyl bromide, methyl chloride, ethyl iodide and ethyl chloride), a di(lower alkyl) sulphate (for example,

dimethyl sulphate and diethyl sulphate) or a lower-alkyl arylsulphonate (for example methyl *paratoluenesulphonate*).

The anion of the novel quinazoline derivatives aforesaid can be derived from any of the well-known organic or inorganic acids. Thus it can be an anion derived from the quaternizing agent used in the foregoing process or it can be a different anion which can be obtained, if desired, by exchange with a salt of a mineral acid (such as a hydrohalic acid, sulphuric acid or phosphoric acid) or an organic acid (such as *paratoluenesulphonic acid*, maleic acid or tartaric acid).

The novel quinazoline derivatives of formula I are converted into the benzdiaz-[1,4]epine 4 - oxide of formula II by reaction with ammonia or a primary amine of the general formula



wherein R⁸ has the significance given earlier.

The reaction of a quinazoline derivative of formula I with ammonia or a primary amine of formula V [i.e. a lower-alkyl amine, a lower-alkenyl amine, a lower-alkynyl amine or a (lower *cycloalkyl*)-(lower alkyl) amine] can be carried out in the presence of an inert solvent such as water, an alkanol or an ether (e.g. tetrahydro-pyran and dioxan) or, if desired, it can be carried out using the amine reactant as the reaction solvent. The reaction is preferably carried out at about room temperature or at a temperature slightly above room temperature. It can be carried out at higher or lower temperatures, suitably at a temperature within the range of from minus 60°C to 150°C. The preferred primary amine of formula V is methyl amine.

The benzdiaz[1,4]epine 4 - oxides of formula II hereinbefore in which R³ (when present) represents a halogen atom or a lower-alkyl group, R⁴ (when present) is in the 8-position and represents a halogen atom or a lower-alkyl group, R⁵ (when present) represents a halogen atom or the nitro group or a lower-alkoxy group, R⁶ is absent and R⁸ (when present) represents a lower-alkyl or lower-alkenyl group are claimed *per se* in the specification of our Letters Patent No. 864,824. The benzdiaz[1,4]epine 4 - oxides of formula II in which one of R³ and R⁴ is present and represents the trifluoromethyl group (R⁴ being in the 8-position when present), R⁵ and R⁶ are absent and R⁸ (when present) represents a lower-alkyl group are claimed *per se* in the specification of our Letters Patent No. 972,969. The benzdiaz[1,4]epine 4-oxides of formula II in which R³ is present and represents the nitro group, R⁴, R⁵ and R⁶ are absent, R⁵ (when present) represents a halogen atom and R⁸ (when pre-

sent) represents a lower-alkyl group are claimed *per se* in the specification of our Letters Patent No. 986,903.

- 5 The following Examples illustrate the process and conversion provided by the invention:

EXAMPLE 1

A) The process:

- 10 A solution of 5.0 g (15.9 mmol) of 6-chloro - 2 - dimethylaminomethyl - 4-phenyl - quinazoline 3 - oxide in 50 ml of methanol was treated at room temperature with 5.0 ml (11.35 g, 80 mmol) of methyl iodide. The product soon crystallized and was collected after cooling in an ice-bath, giving
- 15 [(6 - chloro - 4 - phenyl - 2 - quinazolinyl)-methyl] - trimethyl - ammonium iodide 3-oxide as yellow prisms of melting point 199°—201°C (with decomposition). Further recrystallizations from methanol raised the
- 20 melting point to 201°—203°C (with decomposition).

B) The conversion:

- 25 (i) 1 g (2.19 mmol) of [(6 - chloro - 4-phenyl - 2 - quinazolinyl) - methyl] - trimethyl - ammonium iodide 3 - oxide was allowed to react with ca. 20 ml of liquid methyl amine in a sealed tube for 19 days at 25°—28°C. After this time the tube
- 30 was opened and the excess methyl amine allowed to evaporate. The residue was extracted with 15 ml of hot methanol, the solution was filtered and evaporated *in vacuo* and the resulting residue was partitioned between ice-cold dilute hydrochloric acid and ether.
- 35 The aqueous-acid layer was carefully made basic with dilute sodium hydroxide solution and the precipitated 7 - chloro - 2 - methylamino - 5 - phenyl - 3H - benzdia[1,4]epine 4-oxide was recovered by extraction with methylene chloride to give an orange-yellow crystalline residue. Trituration with
- 40 acetone gave 7 - chloro - 2 - methylamino - 5 - phenyl - 3H - benzdia[1,4]epine 4-oxide as pale yellow plates of melting point 236°—238°C.

The same reaction was also carried out at minus 5°C to minus 10°C for 6 hours.

- 50 (ii) 0.77 g (1.69 mmol) of [(6 - chloro - 4 - phenyl - 2 - quinazolinyl) - methyl] - trimethyl - ammonium iodide 3-oxide was treated with 12 per cent methyl amine in 25 ml of methanol and the product was isolated in the manner described in Example 2C hereinafter to give 7 - chloro - 2 - methylamino - 5 - phenyl - 3H - benzdia[1,4]epine 4-oxide of melting point
- 55 235°—237°C.

EXAMPLE 2

- 60 A) The preparation of the starting material:

30.5 g (0.10 mol) of 6 - chloro - 2-chloromethyl - 4 - phenyl - quinazoline 3-oxide were added portionwise to a stirred solution of 70 g (0.07 mol) of hexa-

methylenimine in 120 ml of methanol during 30 minutes at room temperature. Stirring was continued for a further 16 hours, then the mixture was concentrated *in vacuo* at <30°C, diluted with water and acidified with hydrochloric acid. The solution was extracted with ether to remove non-basic impurities and then the acid aqueous layer was cooled and made basic with dilute sodium hydroxide solution. The crude product precipitated and was recovered by extraction with methylene chloride. Recrystallization from (methylene chloride)/hexane gave 6 - chloro - 2 - [(hexahydro - azepinyl)-(1)] - methyl - 4 - phenyl - quinazoline 3-oxide of melting point 98°—100°C. Further recrystallizations from ether/(petroleum ether) afforded yellow needles of melting point 99°—101°C.

B) The process

To a stirred solution of 5.0 g (13.55 mmol) of 6 - chloro - 2 - [(hexahydro - azepinyl)-(1)] - methyl - 4 - phenyl - quinazoline 3-oxide in 100 ml of acetone were added at room temperature 4.24 ml (9.66 g, 68 mmol) of methyl iodide. The product precipitated and was collected and washed with acetone and ether. Recrystallization from methanol/ethanol gave 1 - [(6 - chloro - 4 - phenyl - 2 - quinazolinyl) - methyl] - 1 - methylhexahydroazepinium iodide N³-oxide of melting point 208°—210°C (with decomposition). Further recrystallizations from methanol afforded yellow prisms of melting point 205°—207°C (with decomposition).

C) The conversion:

1.0 g (1.96 mmol) of 1 - [(6 - chloro - 4 - phenyl - 2 - quinazolinyl) - methyl] - 1-methyl - hexahydroazepinium iodide N³-oxide was added portionwise to a stirred 12 per cent solution of methyl amine in 20 ml of methanol at room temperature. The mixture was stirred for a further 69 hours and was then filtered. The filtrate was evaporated and the resulting residue was extracted with a mixture of dilute hydrochloric acid and ether. The aqueous acid layer was filtered and made basic with dilute sodium hydroxide solution. Extraction with methylene chloride afforded 7 - chloro - 2 - methylamino - 5-phenyl - 3H - benzdia[1,4]epine 4-oxide. Trituration with acetone gave pale yellow prisms of melting point 234°—237°C.

The following preparations illustrate the manner in which other tertiary amines useful in the process provided by the invention can be obtained:

Preparation A:

Reaction of 6 - chloro - 2 - chloromethyl - 4 - piperidine in methanol and isolation of the product in the manner described in Example 2A) gave 6 - chloro - 4 - phenyl - 2-

piperidinomethyl - quinazoline 3-oxide. A sample was recrystallized from acetone as colourless needles of melting point 151°—153°C.

5 Preparation B:

Reaction of 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3-oxide with a solution of morpholine in methanol and isolation of the product in the manner described in Example 2A) gave 6 - chloro - 2 - morpholinomethyl - 4 - phenyl - quinazoline 3-oxide. A sample was recrystallized from aqueous methanol as pale yellow prisms of melting point 184°—185°C.

15 Preparation C:

5.0 g (16.4 mmol) of 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3-oxide were added portionwise to a stirred mixture of 50 ml of ethylenimine and 14 ml of triethyl amine at 0°C. After 1.5 hours at 0°C, the precipitated product was recovered by filtration and washed with petroleum ether. Recrystallization from (methylene chloride)/hexane gave 6 - chloro - 2 - ethyleniminomethyl - 4 - phenyl - quinazoline 3-oxide as pale yellow needles of melting point 169°—171°C.

Preparation D:

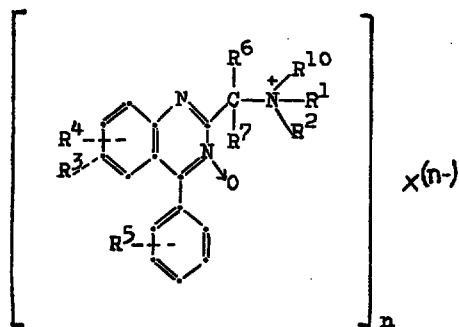
6 - Chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3-oxide was reacted with a solution of pyrrolidine in methanol and the product was isolated as described in Example 2A) to give 6 - chloro - 2 - [(1' - pyrrolidinyl) - methyl] - phenyl - quinazoline 3-oxide as pale yellow needles of melting point 159°—161°C (with decomposition).

The 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3-oxide referred to in Example 2 and the foregoing preparations is claimed *per se* in the specification of our Letters Patent No. 864,825.

Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patent No. 1,043,152.

WHAT WE CLAIM IS:—

1) Quinazoline derivatives of the general formula



wherein R¹ and R² each represent a lower-alkyl group or together represent a lower-alkylene, aza-(lower alkylene), N-(lower alkyl)-aza-(lower alkylene), oxa-(lower alkylene) or thia-(lower alkylene) group, R³, R⁴ and R⁵ each represent a halogen atom or the trifluoromethyl, nitro or cyano group or a lower-alkyl or lower-alkoxy group, R⁶ and R⁷ each represent a hydrogen atom or a lower-alkyl group, R¹⁰ represents a lower-alkyl or aralkyl group, *n* is an integer and X⁽ⁿ⁻⁾ represents an anion of an acid having *n* displaceable hydrogen atoms and wherein the broken lines denote that the groups or atoms attached thereby are optional.

2) Derivatives as formulated in Claim 1, wherein R⁴ and R⁵ are absent and R⁶ and R⁷ each represent a hydrogen atom.

3) Derivatives as formulated in claim 1, wherein R⁴ and R⁵ are absent, R⁶ and R⁷ each represent a hydrogen atom and R³ is present and represents a chlorine atom.

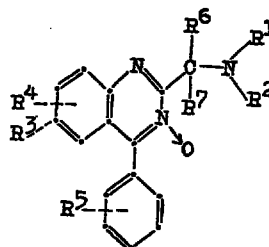
4) Derivatives as formulated in claim 1, wherein R⁴ and R⁵ are absent, R⁶ and R⁷ each represent a hydrogen atom, R³ is present and represents a chlorine atom and R¹ and R² together represent an ethylene, propylene, butylene, pentamethylene or hexamethylene group.

5) Derivatives as formulated in claim 1, wherein R⁴ and R⁵ are absent, R⁶ and R⁷ each represent a hydrogen atom, R³ is present and represents a chlorine atom and R¹ and R² together represent a 3 - oxa - pentamethylene group.

6) Derivatives as formulated in claim 1, wherein R⁴ and R⁵ are absent, R⁶ and R⁷ each represent a hydrogen atom, R³ is present and represents a chlorine atom and R¹, R² and R¹⁰ each represent a methyl group.

7) A pharmaceutical preparation comprising a quinazoline derivative as set forth in any one of the preceding claims in admixture with a compatible pharmaceutical carrier.

8) A process for the manufacture of the quinazoline derivatives formulated in claim 1, which process comprises treating a tertiary amine of the general formula



wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and the broken lines have the significance given in claim 1, with a quaternizing agent and, if desired, exchanging the resulting quaternary salt anion with a different anion.



piperidinomethyl - quinazoline 3-oxide. A sample was recrystallized from acetone as colourless needles of melting point 151°—153°C.

5 Preparation B:

Reaction of 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3-oxide with a solution of morpholine in methanol and isolation of the product in the manner described in Example 2A) gave 6 - chloro - 2 - morpholinomethyl - 4 - phenyl - quinazoline 3-oxide. A sample was recrystallized from aqueous methanol as pale yellow prisms of melting point 184°—185°C.

15 Preparation C:

5.0 g (16.4 mmol) of 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3-oxide were added portionwise to a stirred mixture of 50 ml of ethylenimine and 14 ml of triethyl amine at 0°C. After 1.5 hours at 0°C, the precipitated product was recovered by filtration and washed with petroleum ether. Recrystallization from (methylene chloride)/hexane gave 6 - chloro - 2 - ethyleniminomethyl - 4 - phenyl - quinazoline 3-oxide as pale yellow needles of melting point 169°—171°C.

Preparation D:

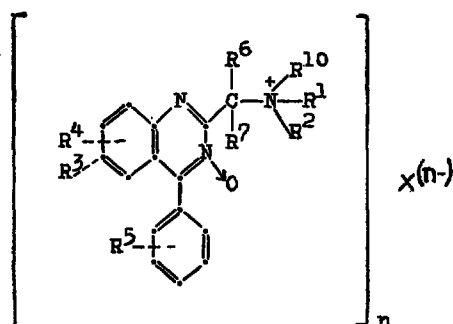
6 - Chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3-oxide was reacted with a solution of pyrrolidine in methanol and the product was isolated as described in Example 2A) to give 6 - chloro - 2 - [(1' - pyrrolidinyl) - methyl] - phenyl - quinazoline 3-oxide as pale yellow needles of melting point 159°—161°C (with decomposition).

The 6 - chloro - 2 - chloromethyl - 4 - phenyl - quinazoline 3-oxide referred to in Example 2 and the foregoing preparations is claimed *per se* in the specification of our Letters Patent No. 864,825.

Having regard to the provisions of Section 9 of the Patents Act, 1949, attention is directed to the claims of Patent No. 1,043,152.

WHAT WE CLAIM IS:—

1) Quinazoline derivatives of the general formula



wherein R¹ and R² each represent a lower-alkyl group or together represent a lower-alkylene, aza-(lower alkylene), N-(lower alkyl)-aza-(lower alkylene), oxa-(lower alkylene) or thia-(lower alkylene) group, R³, R⁴ and R⁵ each represent a halogen atom or the trifluoromethyl, nitro or cyano group or a lower-alkyl or lower-alkoxy group, R⁶ and R⁷ each represent a hydrogen atom or a lower-alkyl group, R¹⁰ represents a lower-alkyl or aralkyl group, n is an integer and X⁽ⁿ⁻⁾ represents an anion of an acid having n displaceable hydrogen atoms and wherein the broken lines denote that the groups or atoms attached thereby are optional.

2) Derivatives as formulated in Claim 1, wherein R⁴ and R⁵ are absent and R⁶ and R⁷ each represent a hydrogen atom.

3) Derivatives as formulated in claim 1, wherein R⁴ and R⁵ are absent, R⁶ and R⁷ each represent a hydrogen atom and R³ is present and represents a chlorine atom.

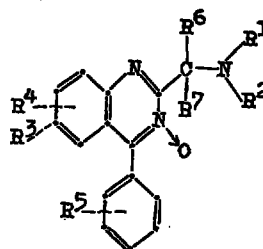
4) Derivatives as formulated in claim 1, wherein R⁴ and R⁵ are absent, R⁶ and R⁷ each represent a hydrogen atom, R³ is present and represents a chlorine atom and R¹ and R² together represent an ethylene, propylene, butylene, pentamethylene or hexamethylene group.

5) Derivatives as formulated in claim 1, wherein R⁴ and R⁵ are absent, R⁶ and R⁷ each represent a hydrogen atom, R³ is present and represents a chlorine atom and R¹ and R² together represent a 3 - oxa - pentamethylene group.

6) Derivatives as formulated in claim 1, wherein R⁴ and R⁵ are absent, R⁶ and R⁷ each represent a hydrogen atom, R³ is present and represents a chlorine atom and R¹, R² and R¹⁰ each represent a methyl group.

7) A pharmaceutical preparation comprising a quinazoline derivative as set forth in any one of the preceding claims in admixture with a compatible pharmaceutical carrier.

8) A process for the manufacture of the quinazoline derivatives formulated in claim 1, which process comprises treating a tertiary amine of the general formula



wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷ and the broken lines have the significance given in claim 1, with a quaternizing agent and, if desired, exchanging the resulting quaternary salt anion with a different anion.

9) A process as set forth in claim 8, wherein a tertiary amine in which R⁴ and R⁵ are absent and R⁶ and R⁷ each represent a hydrogen atom is used as the starting material.

10) A process as set forth in claim 8 wherein a tertiary amine in which R⁴ and R⁵ are absent and R⁶ and R⁷ each represent a hydrogen atom and R³ is present and represents a chlorine atom is used as the starting material.

11) A process as set forth in claim 8 wherein a tertiary amine in which R⁴ and R⁵ are absent and R⁶ and R⁷ each represent a hydrogen atom, R³ is present and represents a chlorine atom and R¹ and R² together represent an ethylene, propylene, butylene, pentamethylene or hexamethylene group is used as the starting material.

12) A process as set forth in claim 8, wherein a tertiary amine in which R⁴ and R⁵ are absent and R⁶ and R⁷ each represent a hydrogen atom, R³ is present and represents a chlorine atom and R¹ and R² together represent a 3 - oxa - pentamethylene group is used as the starting material.

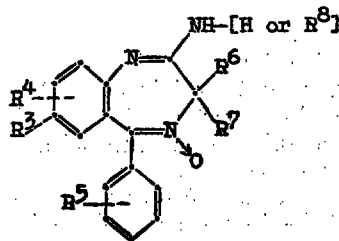
13) A process as set forth in claim 8, wherein 6 - chloro - 4 - phenyl - 2 - dimethylaminomethyl - quinazoline 3-oxide is used as the tertiary amine starting material and is treated with a methyl quaternising agent.

14) A process as set forth in claim 8, substantially as described with reference to part A) of Example 1 and part B) of Example 2.

15) Quinazoline derivatives as formulated in claim 1, when manufactured by the process claimed in any one of claims 8 to 14 inclusive.

16) A process for the production of benz-

diaz[1,4]epine 4-oxides of the general formula



wherein R³, R⁴, R⁵, R⁶, R⁷ and the broken lines have the significance given in claim 1 and R⁸ represents a lower-alkyl, lower-alkenyl, lower-alkynyl or (lower cycloalkyl)-(lower alkyl) group, which comprises reacting a quinazoline derivative as claimed in claim 1 or claim 15 with ammonia or a primary amine of the general formula



wherein R⁸ has the significance given earlier in this claim.

17) A process as set forth in claim 16, wherein said primary amine is methylamine.

18) A process as set forth in claim 16, substantially as described with reference to part C) of Examples 1 and 2.

19) Benzdiaz[1,4]epine 4-oxides of the formula first written in claim 16, when manufactured by the process claimed in claim 16, claim 17 or claim 18.

W. D. WHITAKER,
Patent Agent

for F. HOFFMANN-LA ROCHE & CO.,
Aktiengesellschaft.

