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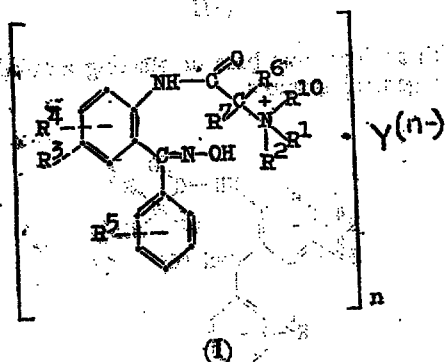
COMPLETE SPECIFICATION

Novel Oximes and a Process for the Manufacture and Conversion thereof

We, F. HOFFMAN-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:—

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

The novel oximes provided by the invention may be formulated thus:



15 wherein R¹ and R³ 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, 20 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

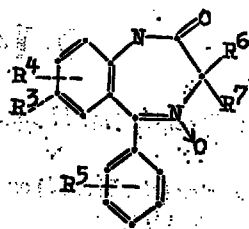
[Price 4s. 6d.]

aralkyl group, n is an integer and $Y^{(n-)}$ represents the anion of an acid having a displaceable hydrogen atoms or, where n stands for 1, a hydroxide ion and wherein the broken lines denote that the groups or atoms attached thereby are optional.

The novel oximes 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 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 oximes provided by the invention.

The novel oximes aforesaid in which $Y^{(n-)}$ represents a hydroxide ion are also useful in that they can be converted in a manner to be described hereinafter into pharmaceutically useful benzodiaz[1,4]epinone - (2) - 4 - oxides of the general formula

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(II)

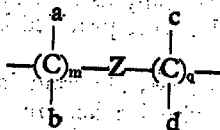
wherein R^3 , R^4 , R^5 , R^6 , R^7 are broken lines have the significance given earlier.

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 alkoxy' is used to mean a straight-chain or branched-chain alkoxy group containing from one to seven carbon atoms. The symbols R^3 and R^4 , 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 group 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

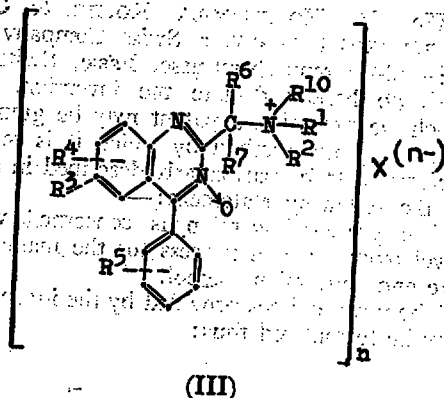


wherein the symbols a , b , c and d each represent a hydrogen atom or a lower-alkyl group and can be the same or different, Z represents an oxygen or sulphur atom or an NH group which may carry a lower-alkyl group as a substituent and m and q each stand for 1, 2, 3

or 4 provided that the sum of m and q is not greater than 5. The terms 'halogen' means iodine, bromine, chlorine or fluorine. Chlorine and fluorine are preferred. The aralkyl group is preferably a benzyl group.

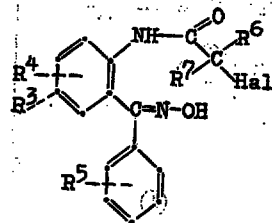
The most interesting oximes of formula I hereinbefore are those in which R^4 and R^5 are absent and R^6 and R^7 each represent a hydrogen atom, particularly those in which R^3 is present and represents a chlorine atom. The preferred oximes of formula I hereinbefore are 2' - benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methohydroxide oxime, the 2' - benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methohalide oximes and the (2 - benzoyl - 4 - chloro - phenyl) - carbamoylmethyl trimethyl ammonium oxide salts.

According to the process provided by the invention, the novel oximes aforesaid are manufactured either by treating a quinazoline derivative of the general formula



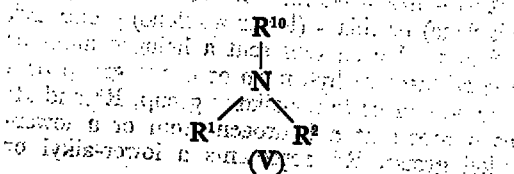
(III)

with an inorganic base or reacting a halide of the general formula

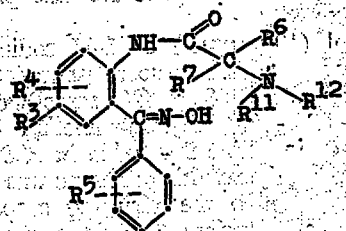


(IV)

with an amine of the general formula



or exhaustively alkylating an amine of the general formula



(VI)

with an alkylating or quaternising agent and, in any case where required, converting any base obtained into a salt or any salt obtained into the base or a different salt; in which formulae n , R^1 , R^2 , R^3 , R^4 , R^5 , R^6 , R^7 , R^{10} and the broken lines have the significance given earlier, R^{11} and R^{12} each represent a hydrogen atom or 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, $X^{(a)}$ represents the anion of an acid having n displaceable hydrogen atoms and Hal stands for a halogen atom.

The most interesting starting materials of formulae III, IV and VI hereinbefore are those in which R^4 and R^5 are absent and R^6 and R^7 each represent a hydrogen atom, particularly those in which R^3 is present and represents a chlorine atom.

According to one embodiment of the foregoing process, a quinazoline derivative of formula III is treated with an inorganic base.

Any suitable inorganic base such as an alkali-metal or alkaline-earth-metal base (e.g. sodium hydroxide, potassium hydroxide or barium hydroxide) can be used. A preferred aspect of this embodiment comprises treating a [6-chloro - 4 - phenyl - quinazolinyl - (2) - methyl] trimethyl ammonium 3-oxide salt with an inorganic base.

According to another embodiment of the foregoing process, a halide of formula IV is reacted with an amine of formula V. A preferred aspect of this embodiment comprises reacting a 2' - benzoyl - 4' - chloro - 2 - halo - acetanilide oxime with trimethyl amine. The halide used in this embodiment is preferably a bromide, chloride or iodide. The most preferred halides are the iodides as, in general, iodides are the most reactive. Indeed, in some cases it is advantageous to convert a chloride or bromide into an iodide.

According to yet another embodiment of the foregoing process, an amine of formula VI is converted into a quaternary ammonium salt by exhaustive alkylation. This can be accomplished by any of the usual techniques for quaternising amines; for example, treatment of the corresponding tertiary amine with a quaternising agent such as, for example, a lower alkyl halide (e.g. methyl iodide, methyl bromide, methyl chloride, ethyl iodide or ethyl

chloride), a di(lower-alkyl) sulphate (e.g. dimethyl sulphate or diethyl sulphate) or a lower-alkyl arylsulphonate (e.g. methyl *para*-toluenesulphonate). A preferred aspect of this embodiment comprises exhaustively methylating a 2' - benzoyl - 4' - chloro - 2 - (amino or methylamino or dimethylamino)-acetanilide oxime.

The anion denoted by $Y^{(a)}$ in formula I can be derived from any of the well-known organic or inorganic acids. Thus, for example, it can be the anion derived from the quaternising agent employed in the foregoing process or it can be a different anion which can be obtained, if desired, by exchange with a different acid. The anion $Y^{(a)}$ is preferably a pharmaceutically acceptable anion such as an anion derived from a mineral acid (e.g. a hydrohalic acid, sulphuric acid and phosphoric acid) or an organic acid (e.g. *para*-toluenesulphonic acid, maleic acid and tartaric acid).

The quinazoline derivatives of formula III hereinbefore and a process for their preparation are claimed in the specification of our copending Application for Letters Patent No. 1580/67 (now Serial No. 1144515).

The oximes of formula I in which $Y^{(a)}$ represents a hydroxide ion are converted into the benzdiaz[1,4]epinone - (2) 4 - oxides of formula II by heating.

The oximes of formula I exist in *syn* and *anti* configuration and the heating, which may also be described as an intramolecular condensation, can be carried out using a mixture of both forms although the *anti* form is preferred. The condensation is readily carried out at a temperature of from 20°C to 250°C, preferably at a temperature between 20°C and the reflux temperature of the condensation mixture.

It will be appreciated that an oxime of formula I in which $Y^{(a)}$ represents a hydroxide ion, manufactured by treating a quinazoline derivative of formula III with a base, can be heated without isolation from the medium in which it is manufactured to give a corresponding benzdiaz[1,4]epinone - (2) 4 - oxide of formula II.

The benzdiaz[1,4]epinone - 2 4 - oxides of formula II in which R^3 and R^4 (when present) each represent a halogen atom or the trifluoromethyl or nitro group or a lower-alkyl or lower-alkoxy group (provided that R^3 and R^4 cannot both represent a trifluoromethyl group), R^5 (when present) represents a halogen atom or the trifluoromethyl group or a lower-alkyl or lower-alkoxy group and R^7 represents a hydrogen atom are claimed *per se* in the specification of our letters patent No. 972,968.

The following Example illustrates the process and conversion provided by the invention:

EXAMPLE

A) The process:

i) 2 g (4.38 mmol) of [6 - chloro - 4 - phenyl - quinazolinyl - (2) - methyl] trimethyl ammonium iodide 3-oxide [prepared as described in the specification of our co-pending Application No. 1580/67 (now Serial No. 1144515)] were added portionwise to a mixture of 13.1 ml (13.1 mmol) of 1-N sodium hydroxide solution and 27 ml of water at room temperature during 1 hour. The resulting solution was stirred for 17 hours, then acidified (pH 5—6) with dilute hydriodic acid. The resulting crystalline precipitate was filtered off and recrystallized from (methylene chloride)/hexane to give 2' - benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methiodide *antioxime* of melting point 196°—198°C. Further recrystallizations from methanol afforded colourless needles of melting point 207°—209°C (with decomposition).

ii) A solution of 29.6 g (91.6 mmol) of 2' - benzoyl - 2,4' - dichloro - acetanilide *antioxime* and 15.3 g (102 mmol) of sodium iodide in 620 ml of acetone was stirred and heated to reflux for 30 minutes. After cooling, water was added until all of the precipitated salt had dissolved. On further addition of water the solution became turbid and 2' - benzoyl - 4' - chloro - 2 - iodo - acetanilide *antioxime* crystallized. It was filtered off and recrystallized from a mixture of methylene chloride and hexane; melting point = 130°—131°C. (with decomposition).

A suspension of 2.08 g (5 mmol) of 2' - benzoyl - 4' - chloro - 2 - iodo - acetanilide *antioxime* in 25 ml of methanol was added slowly at room temperature to a stirred solution of 2.7 g (46 mmol) of dry trimethyl amine in 20 ml of methanol. Stirring was continued for 24 hours, then the solution was evaporated at 25°—30°C *in vacuo*. Recrystallization of the residue from methanol/ether gave 2' - benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methiodide *antioxime* of melting point 191°—195°C (with decomposition). Further recrystallizations gave colourless needles of melting point 210°C (with decomposition).

iii) 6.23 ml (14.2 g, 100 mmol) of methyl iodide were added dropwise at room temperature during 1.5—2 hours to a stirred suspension of 10 g (30.1 mmol) of 2' - benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide *antioxime* in 100 ml of methanol. The resulting mixture was stirred for 2 hours, then heated on the steam-bath and diluted with methanol until all dissolved. Concentration and addition of ether gave 2' - benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methiodide *antioxime* as pale yellow needles of melting point 208°—210°C (with decomposition).

[2' - benzoyl - 4' - chloro - 2 - dimethyl-

amino - acetanilide *antioxime* was prepared as follows:

100 ml (100 mmol) of 1-N sodium hydroxide were added at room temperature to a solution of 15.69 g (50 mmol) of 6 - chloro - 2 - dimethylaminomethyl - 4 - phenyl - quinazoline 3 - oxide in 250 ml of methanol and the resulting mixture was stirred for 17 hours. To the resulting suspension, containing a colourless precipitate, there was added excess solid carbon dioxide and the mixture was concentrated at 25°C *in vacuo* and diluted with water. The precipitate was filtered off and washed with water. Recrystallizations from methanol gave 2' - benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide *antioxime* as colourless prisms of melting point 190°—192°C].

A solution of 10 g (21 mmol) of 2' - benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methiodide *antioxime* in 300 ml of 80% methanol/water was filtered slowly through a 210×19 mm (diameter) column of DOWEX AG 1-X8 (100—200 mesh, hydroxide form) anion exchange resin which had been previously washed with 80% methanol/water (the word 'DOWEX' is a Registered Trade Mark). Evaporation of the eluate at less than 30°C *in vacuo* and recrystallization from water gave 2' - benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methohydroxide *antioxime* as cream coloured prisms of melting point 111°—114°C (with decomposition).

B) The conversion:

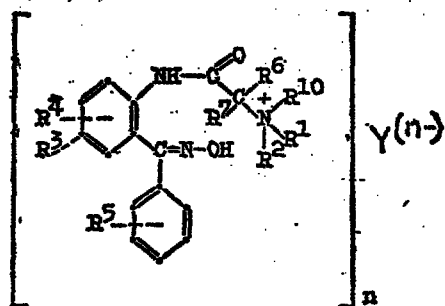
0.5 g (1.37 mmol) of 2' - benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methohydroxide *antioxime* were heated in an open test tube immersed in an oilbath at 120°—125°C for 5 minutes. The compound melted to a toffee-like consistency and much trimethyl amine was evolved. The temperature was then raised to 155°C during a period of 10 minutes until no further amine was evolved. The resulting mixture was cooled, methylene chloride and water were added, the so-obtained mixture was acidified with dilute acetic acid (pH 6) and the methylene chloride phase was separated from the aqueous phase. The residue obtained on evaporation of the methylene chloride phase was extracted with cold dilute sodium hydroxide solution and the extract was acidified (pH 5) with dilute acetic acid. The precipitated 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - benzodiaz-[1,4]epinone - (2) 4 - oxide was recovered by extraction with methylene chloride and obtained as a pale yellow gum. Trituration with acetone gave colourless needles of 7 - chloro - 5 - phenyl - 2,3 - dihydro - 1H - benzodiaz-[1,4]epinone - (2) 4 - oxide of melting point 235°—238°C.

7 - Chloro - 5 - phenyl - 2,3 - dihydro - 1H - benzodiaz[1,4] - epinone - (2) 4 - oxide

could also be obtained by heating 2'-benzoyl - 4'-chloro - 2 - dimethylamino - acetanilide methohydroxide oxime at 200°—205°C for 4 minutes or by heating said oxime in tetralin or quinoline solution at 200°—210°C for 2 hours.

WHAT WE CLAIM IS:—

1) Oximes of the general formula



- 10 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 Y⁽ⁿ⁻⁾ represents the anion of an acid having n displaceable hydrogen atoms or, where n stands for 1, a hydroxide ion and wherein the broken lines denote that the groups of atoms attached thereby are optional.

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

- 30 3) Oximes 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.

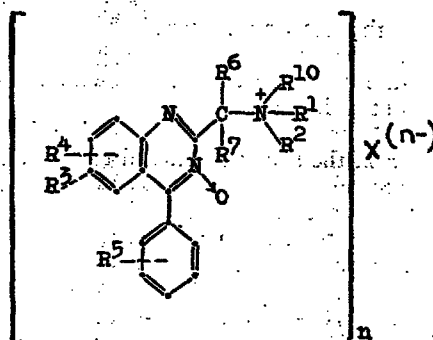
4) 2' - Benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methohydroxide oxime.

- 35 5) A 2' - Benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methohalide oxime.

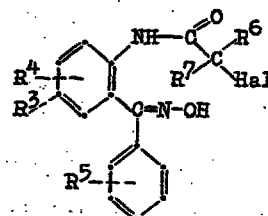
6) A (2 - benzozy - 4 - chloro - phenyl) - carbamoylmethyl trimethyl ammonium oxime salt.

- 40 7) A pharmaceutical preparation comprising an oxime as set forth in any one of the preceding claims in admixture with a compatible pharmaceutical carrier.

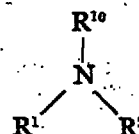
- 45 8) A process for the manufacture of the oximes claimed in claim 1, which process comprises either treating a quinazoline derivative of the general formula



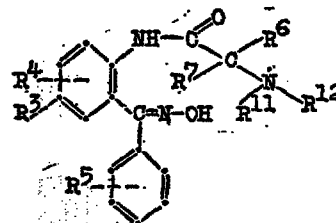
with an organic base or reacting a halide of the general formula



with an amine of the general formula



or exhaustively alkylating an amine of the general formula

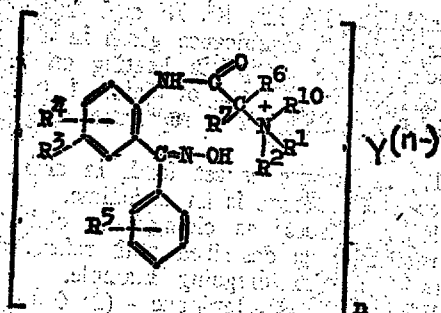


with an alkylating or quaternising agent and, in any case where required, converting any base obtained into a salt or any salt obtained into the base or a different salt; in which formulae n, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R¹⁰ and the broken lines have the significance given in claim 1, R¹¹ and R¹² each represent a hydrogen atom or 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, X⁽ⁿ⁻⁾ represents the anion of an acid having n displaceable hydro-

could also be obtained by heating 2'-benzoyl - 4'-chloro - 2 - dimethylamino - acetanilide methohydroxide antioxime at 200°—205°C for 4 minutes or by heating said oxime in tetralin of quinoline solution at 200°—210°C for 2 hours.

WHAT WE CLAIM IS:—

1) Oximes of the general formula



10 wherein R¹ and R³ 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 Y⁽ⁿ⁻⁾ represents the anion of an acid having *n* displaceable hydrogen atoms or, where *n* stands for 1, a hydroxide ion and wherein the broken lines denote that the groups of atoms attached thereby are optional.

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

3) Oximes 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.

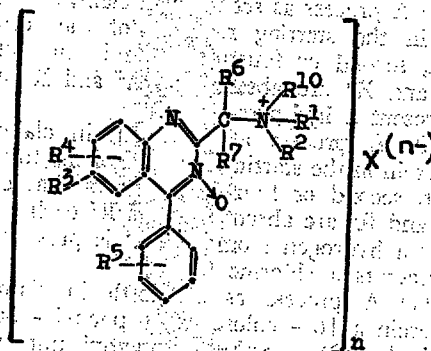
4) 2' - Benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methohydroxide oxime.

5) A 2' - Benzoyl - 4' - chloro - 2 - dimethylamino - acetanilide methohalide oxime.

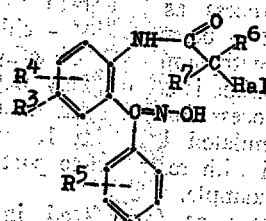
6) A (2 - benzoyle - 4 - chloro - phenyl) - carbamoylmethyl trimethyl ammonium oxime salt.

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

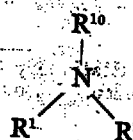
8) A process for the manufacture of the oximes claimed in claim 1, which process comprises either treating a quinazoline derivative of the general formula



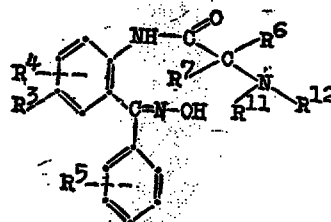
with an organic base or reacting a halide of the general formula



with an amine of the general formula



or exhaustively alkylating an amine of the general formula



with an alkylating or quaternising agent and, in any case where required, converting any base obtained into a salt or any salt obtained into the base or a different salt; in which formulae *n*, R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R¹⁰ and the broken lines have the significance given in claim 1, R¹¹ and R¹² each represent a hydrogen atom or 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, X⁽ⁿ⁻⁾ represents the anion of an acid having *n* displaceable hydro-



gen atoms and Hal stands for a halogen atom.

- 9) A process as set forth in claim 8, wherein in the starting material of the formula first, second or fourth written in that claim R^4 and R^5 are absent and R^6 and R^7 each represent a hydrogen atom.

- 10) A process as set forth in claim 8, wherein in the starting material of the formula first, second or fourth written in that claim R^4 and R^5 are absent, R^6 and R^7 each represent a hydrogen atom and R^3 is present and represents a chlorine atom.

- 11) A process as set forth in claim 8, wherein a [6-chloro-4-phenyl-quinazolinyl-(2)-methyl] trimethyl ammonium 3-oxide salt is treated with an inorganic base.

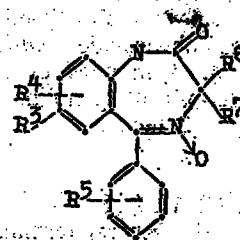
- 12) A process as set forth in claim 8, wherein a 2'-benzoyl-4'-chloro-2-halo-acetanilide oxime is reacted with trimethyl amine.

- 13) A process as set forth in claim 8, wherein a 2'-benzoyl-4'-chloro-2-(amino or methylamino or dimethylamino)-acetanilide oxime is exhaustively methylated.

- 14) A process for the manufacture of the oximes formulated in claim 1, substantially as described with reference to part A) of the foregoing Example.

- 15) Oximes 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]epinone-(2) 4-oxides of the general formula



wherein R^3 , R^4 , R^5 , R^6 , R^7 and the broken lines have the significance given in claim 1, which process comprises heating an oxime as claimed in any one of claims 1 to 6 or claim 15 in which $Y^{(M)}$ represents a hydroxide ion.

- 17) A process as set forth in claim 16, wherein said oxime is an *antioxime*.

- 18) A process as claimed in claim 16, substantially as described with reference to part B) of the foregoing Example.

- 19) Benz-diaz[1,4]epinone-(2) 4-oxides as formulated in claim 16, when manufactured by the process claimed in claim 16, claim 17 or claim 18.

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