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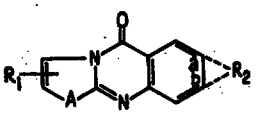
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(54) QUINAZOLONE DERIVATIVES

(71) We, BOEHRINGER INGELHEIM GmbH, a Body Corporate organised under the laws of the Federal Republic of Germany, of Ingelheim am Rhein, Federal Republic of Germany, 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 describd in and by the following statement:—

This invention relates to novel derivatives of quinazolone having interesting pharmacological properties.

According to one feature of the present invention there are provided compounds of general formula



(I)

[wherein A represents a group of the formula

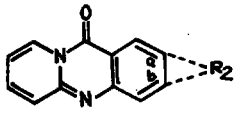
—CH=CH—, —CH=N— or —S—;

R_1 represents a hydrogen atom, an alkyl or alkoxy group containing from 1 to 4 carbon atoms, an amino or acetylamino group, a fused benzene ring, a cyano or tetrazol-5-yl group or a group of the formula —COR_3 (wherein R_3 represents an alkoxy group containing from 1 to 4 carbon atoms, an amino, hydroxylamino or tetrazol-5-yl amino group or, where R_2 as hereinafter defined is other than a hydrogen atom, can additionally represent a hydroxy group); and

R_2 represents a cyano or tetrazol-5-yl group, a group of the formula —COR_4 (wherein R_4 represents an alkoxy group containing from 1 to 4 carbon atoms, a hydroxy, amino, hydroxylamino or tetrazol-5-yl-amino group) or, when R_1 represents a cyano or tetrazol-5-yl group or group of the formula —COR_3 as defined above, can additionally represent a hydrogen atom, an alkyl or alkoxy group each containing from 1 to 4 carbon atoms, an amino or acetylamino group or a fused benzene ring, with the proviso that when A is a group of formula —CH=CH— and R_1 is a hydrogen atom or an alkyl, alkoxy, cyano or tetrazol-5-yl group or a group of the formula —COR_3, then R_2 is other than a hydrogen atom or a cyano, tetrazol-5-yl, alkyl, alkoxy, amino or acetylamino group or a group of the formula —COR_4; and the dotted lines in formula I indicating that R_2 is attached to the *a*- or *b*-positions, where R_2 is other than a fused benzene ring] and the salts thereof.

(It should be noted that the dotted lines in subsequent formulae appearing herein have the same significance as those in formula I).

The invention also includes within its scope copounds of general formula



(Ia)

(wherein R_2 represents a carboxyl, methoxycarbonyl, tetrazol-5-yl-carbamoyl or cyano group; and the dotted lines indicate that R_2 is attached at the *a* or *b* positions) and salts thereof.

The compounds according to the invention and the physiologically acceptable salts thereof possess interesting pharmacological properties. In particular they show an anti-allergic effect and also a muscle-relaxing (e.g. bronchodilating) and vasodilatory activity. The anti-allergic properties of the compounds according to the invention make them suitable for the prophylaxis and treatment of allergic diseases such as, for example, asthma, hay-fever, conjunctivitis, urticaria, eczema and atopic dermatitis. Tests which we have conducted have shown that in the prophylaxis of asthma the compounds of the invention and physiologically acceptable salts thereof subjected to testing have a longer duration of action compared to the known compound cromoglycinic acid and also exhibit an activity when administered orally.

Preferred compounds according to the invention by virtue of their favourable pharmacological properties are compounds in which A represents —CH=CH— or —S—, the group —CH=CH— being particularly preferred; R_1 represents a hydrogen atom, a fused benzene ring, a tetrazol-5-yl group or a group of the formula —COR_3 (wherein R_3 represents a hydroxylamino or tetrazol-5-yl-amino group or, where R_2 is other than a hydrogen atom, can additionally and indeed preferably does represents a hydroxy group);

R_2 represents a tetrazol-5-yl group, a group of the formula —COR_4 (wherein R_4 represents a hydroxy, hydroxylamino or tetrazol-5-yl-amino group) or, when R_1 represents a tetrazol-5-yl group or group of the formula —COR_3 as defined above, can additionally represent a hydrogen atom or a fused benzene ring; and the salts thereof.

Particularly preferred compounds by virtue of their especially favourable phrmacological properties are the following:—

11 - Oxo - 11 - H - pyrido[2,1-b] - quinazoline - 2 - carboxylic acid and the salts thereof;

Ethyl 5 - oxo - 5 - H - thiazolo[2,3 - b]-quinazoline - 7 - carboxylate and the salts thereof;

13 - Oxo - 13 - H - benzo[g] - pyrido-[2,1 - b] - quinazoline - 10 - carboxylic acid and the salts thereof;

11 - Oxo - 11 - H - pyrido[2,1 - b] - quinazoline - 3 - carboxylic acid and the salts thereof;

Methyl 11 - oxo - 11 - H - pyrido[2,1 - b]-quinazoline - 2 - carboxylate and the salts thereof;

11 - Oxo - 11 - H - pyrido[2,1 - b] - N-(1 - H - tetrazol - 5 - yl) - quinazoline - 2-carboxamide and the salts thereof;

2 - Cyano - 11 - oxo - 11 - H - pyrido-[2,1 - b] - quinazoline and the salts thereof.

In compounds of the invention wherein R_1, R_2, R_3 or R_4 represent alkyl or alkoxy groups, these groups preferably contain up to 2 carbon atoms.

It will be appreciated that the salts of compounds of the invention for use in medicine should be physiologically acceptable. Other salts however may be useful in the preparation of the compounds according to the invention or the physiologically acceptable salts thereof.

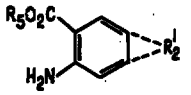
The following processes constitute further features of the present invention

a) for the preparation of compounds of general formula I or Ia (wherein R_1 represents a hydrogen atom, an alkyl or alkoxy group each containing from 1 to 4 carbon atoms, an acetylamino group, a fused benzene ring, or a tetrazol-5-yl or carboxyl group, and R_2 represents a tetrazol-5-yl or carboxyl group or, when R_1 represents a tetrazol-5-yl or carboxyl group, R_2 can additionally represent an alkyl or alkoxy group each containing from 1 to 4 carbon atoms, an acetylamino group or a fused benzene ring) reacting a compound of formula



(II)

(wherein A is as hereinbefore defined; R_1' represents a hydrogen atom, an alkyl or alkoxy group each containing from 1 to 4 carbon atoms, an acetylamino group, a fused benzene ring, or a tetrazol-5-yl or carboxyl group; and X represents a halogen atom) with a compound of formula



(III)

(wherein R_2' represents a tetrazol-5-yl or carboxyl group, an alkoxycarbonyl group containing from 1 to 4 carbon atoms in the alkoxy moiety thereof, or when R_1' represents a tetrazol-5-yl or carboxyl group, can additionally represent an alkyl or alkoxy group each containing from 1 to 4 carbon atoms, an acetylamino group or a fused benzene ring, with the proviso that when A in the compound of formula II represents a group of formula —CH=CH—, and R_1' in the compound of formula II represents a hydrogen atom or an alkyl, alkoxy, tetrazol-5-yl, or carboxy group, then R_2' is other than a tertazol-5-yl, alkyl, alkoxy or acetylamino group or an alkoxycarbonyl group having from 2 to 4 carbon atoms in the alkyl moiety thereof; and R_5 represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms).

In the compounds of formula II X pre-

ferably represents a fluorine, chlorine or bromine atom.

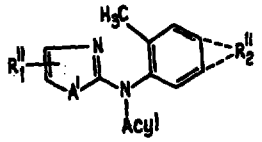
The reaction is preferably effected at an elevated temperature, and advantageously at a temperature of from 120 to 160°C. If desired it may be effected without a solvent or in a high boiling solvent, for example dimethylformamide, or sulfolane. It is useful to add an acid-acceptor, for example an excess of the compound of formula III.

The starting materials used for this process are known and may be obtained by conventional processes.

b) for the preparation of compounds of general formula I, including compounds the subject of the proviso to R_2, (wherein A represents a group of the formula

—CH=CH— or —CH=N—;

R_1 represents a hydrogen atom, an alkoxy group containing from 1 to 4 carbon atoms or a carboxyl group; and R_2 represents a carboxyl group or, when R_1 represents a carboxyl group, can additionally represent an alkoxy group (containing from 1 to 4 carbon atoms) oxidising a compound of formula



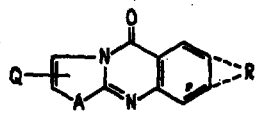
(IV)

(wherein A′ represents a group of the formula —CH=CH— or —CH=N—, R_1'' represents a hydrogen atom, an alkoxy group containing from 1 to 4 carbon atoms or a carboxyl group; and R_2'' represents a methyl or a carboxyl group or, when R_1 represents a carboxyl group, can additionally represent an alkoxy group (containing from 1 to 4 carbon atoms) and subsequently acidifying the compound thereby formed.

The oxidation is generally effected at an elevated temperature with for example, potassium permanganate in an aqueous solution buffered with magnesium sulfate. The acidification may if desired be effected with mineral acids, for example hydrochloric acid, or with organic acids, for example acetic acid.

The starting materials of formula IV for use in this reaction may be produced by conventional methods. If R_1'' and/or R_2'' in the compound of formula IV represent carboxyl groups, the compound may also be produced *in situ* from the corresponding methyl compound or from compounds with other groups convertible, under the reaction conditions, into the carboxyl group.

c) for the preparation of compounds of general formula I (including compounds the subject of the proviso to R_2) converting a compound of formula



(V)

[wherein A is as hereinbefore defined, Q represents the group R_1 or a group readily convertible thereto and R represents the group R_2 or a group readily convertible thereto, at least one of Q and R being a group readily convertible to R_1 or R_2 respectively] into the desired compound of formula I.

Conversion may be effected by conventional methods. For example, compounds of general formula I (wherein R_1 and/or R_2 represent carbamoyl or N - (tetrazol - 5 - yl) - carbamoyl groups) may be prepared from the compound of formula V wherein Q and/or R represent chlorocarbonyl groups by reaction with ammonia or aminotetrazole. Similarly, the corresponding hydroxamic acids and esters of the compounds of general formula I can be prepared by reacting chlorocarbonyl derivatives of the compound V with hydroxylamine or an aliphatic alcohol containing from 1 to 4 carbon atoms respectively. Reacting a compound of formula V wherein Q and/or R represents a cyano group with sodium azide will yield a compound of formula I wherein R_1 and/or R_2 represent tetrazol-5-yl groups. Cyano compounds of formula I may be obtained by dehydration of the corresponding carbamoyl compounds of formula V, and carboxyl compounds by the saponification of compounds of formula V wherein Q and/or R represent ester or amide groups. Carboxyl compounds may also, if desired, be obtained by the oxidation of compounds of formula V wherein Q and/or R represent methyl groups, for example with potassium permanganate. For the preparation of compounds of formula I (wherein R_1 or R_2 represents an amino group), a compound of formula V (wherein Q or R represents an acylamino group) may, for example, be subjected to acid or alkaline saponification.

The products obtained from processes a) to c) may be subsequently converted, if desired, into acid addition salts or, when R_1 and/or R_2 represent carboxyl groups, into salts with organic or inorganic bases. If salts of the compounds are first obtained, the free compounds can readily be liberated by conventional techniques.

Suitable acids for the preparation of acid addition salts of the compounds include, for example, hydrochloric acid, hydrobromic acid, sulphupric acid, phosphoric acid, lactic acid, citric acid and maleic acid. Suitable bases for the preparation of basic salts are for example sodium hydroxide or potassium hydroxide.

In addition to the use of the novel com-

pounds according to the invention directly in medicine, they may also serve as intermediate products for the production of other pharmaceutically active agents.

According to a further feature of the invention there are provided pharmaceutical compositions comprising, as active ingredient, a compound of formula I or Ia as hereinbefore defined or a physiologically acceptable salt thereof in association with a pharmaceutical carrier or excipient.

The pharmaceutical compositions according to the invention can, for example, be in a form suitable for oral, rectal, parenteral, pulmonary or topical administration which forms may alternatively contain a compound the subject of the proviso to R_2 as active ingredient. Suitable forms of administration being, for example, capsules, tablets, coated tablets, solutions, suspensions, aerosols, sterile isotonic solutions, creams, ointments, lotions, emulsions, sprays or suppositories.

If desired, the compositions according to the invention can be in dosage unit form. When administered by the puplmonary route, each dosage unit preferably comprises 20 to 500μg/kg of the active ingredient, for oral administration 1 to 50 mg of the active ingredient and for intravenous administration 0.2 to 10 mg of the active ingredient. For nasal or occular administration each dosage unit preferably comprises 0.5 to 25 mg of active ingredient. In general, the specific dose administered depends on the nature of the condition which is to be treated.

Tablets may, for example, be obtained by mixing the active ingredient with known excipients, for example with inert diluents such as calcium carbonate, magnesium stearate or talcum and/or agents for obtaining sustained release, such as carboxypolymethylene, carboxymethyl cellulose, cellulose acetatephthalate or polyvinyl acetate. The tablets may, if desired, consist of several layers, for example to obtain sustained release or to avoid incompatibilities.

Coated tablets may be obtained by coating tablet cores prepared analogously to the tablets described above, with agents commonly applied for tablet coating, for example, polyvinylpyrrolidone, shellac, gum arabic, talcum, titanium dioxide or sugar. To obtain sustained release or for avoiding incompatibilities the core may also consist of several layers. The tablet coating may also consist of several layers whereby the excipients mentioned above for tablets may be used.

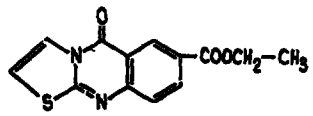
Capsules comprising the active ingredient according to the invention may be produced, for example, by mixing the active ingredient with inert carriers such as lactose or sorbitol and filling gelatin capsules with the mixture.

For pulmonary administration, the active ingredient according to the invention may be conveniently combined with conventional aerosol formulations and filled into spray cans, preferably cans provided with metering means. The active ingredients may also, if desired, be made into aerosol formulations in micronised form (generally with a particle size of 2 to 6μm), optionally with the addition of micronised carriers such as lactose. These formulations may be filled into hard gelatine capsules. Conventional devices for powder inhalation are generally used, and into each capsule preferably 2 to 40 mg of active ingredient and 0 to 40 mg of lactose are filled.

The following examples illustrate the invention:—

Example 1.

Ethyl 5 - oxo - 5 - H - thiazolo[2,3 - b]-quinazoline - 7 - carboxylate



2.4 g of 2-chlorothiazole are heated with 5.6 g of diethyl 4-amino-isophthalate in an oil bath to 150°C for 8 hours. The resulting dark brown oil is then refluxed with 10 ml of acetonitrile for 1 hour, cooled and the crystals obtained removed by suction filtration. By recrystallization from a little methanol the title compound is obtained.

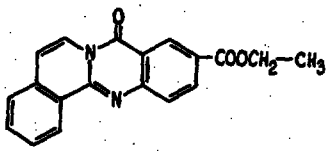
Melting point: 148—155°C (pale yellow needles).

Analysis: $C_{13}H_{10}N_2SO_3$

	C%	H%	N%	S%
calc:	56.93	3.65	10.22	11.68
found:	56.87	3.82	10.21	11.82

Example 2.

Ethyl 8 - oxo - 8 - H - isoquino[1,2 - b] quinazoline - 10 - carboxylate



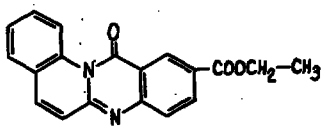
4.97 g of 1-chloroisoquinoline are mixed with 14.4 g of diethyl 4-amino-isophthalate and heated slowly to 150°C. The molten mixture solidifies after about 45 minutes. After addition of 50 ml of ethanol, it is refluxed for 1 hour, cooled and the product removed by suction filtration. The hydrochloride is obtained, from which the free base is liberated in water with the calculated quantity of sodium bicarbonate and extracted with chloroform. After evaporating and purifying the compound over a silica gel column, lemon-yellow crystals are obtained (m.p. 205—210°C.)

Analysis: $C_{19}H_{14}N_2O_3$

	C%	H%	N%
calc:	21.70	4.50	8.81
found:	71.58	4.40	8.68

Example 3.

12 - Oxo - 12 - H - quino[2,1 - b] - quinazoline - 10 - ethyl carboxylate



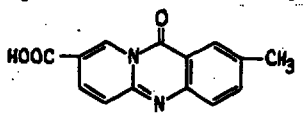
4.1 g of 2-chloroquinoline are reacted with 11.9 g of 4-amino-diethyl isophthalate, as described in Example 2, and worked up. The compound thus obtained has a melting point of 157—163°C.

Analysis: $C_{19}H_{14}N_2O_3$

	C%	H%	N%	O%
calc:	71.70	4.40	8.81	15.09
found:	71.70	4.17	8.67	15.95

Example 4.

11 - Oxo - 11 - H - 2 - metthyl - pyrido[2,1-b] - quinazoline - 8 - carboxylic acid



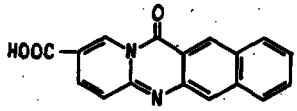
4.3 7g of 6-chloronicotinic acid are heated with 4.53 g of 5-methyl-anthranilic acid to 150°C. After several minutes the reaction product solidifies, it is then boiled with 5 times its volume of concentrated hydrochloric acid, cooled, removed by suction filtration and washed with water and acetonitrile. The resulting hydrochloride is suspended in water and acetonitrile. The resulting hydrochloride is suspended in water and dissolved with the calculated quantity of sodium bicarbonate to produce the free base. On acidifying this solution with acetic acid the desired product precipitates.

Analysis: $C_{24}H_{10}N_2O_3$

	C%	H%	N%
calc:	66.14	3.94	11.02
found:	66.19	4.09	11.11

Example 5.

13 - Oxo - 13 - H - benzo[g] - pyrido[2,1-b] - quinazoline - 10 - carboxylic acid



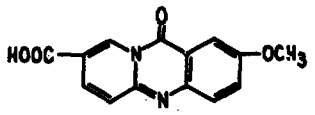
1.32 g of 6-chloronicotinic acid are heated with 1.8 g of ethyl 2-amino-3-naphthoate to 160°C. The melt, solidifying after a short time, is boiled with 100 ml of ethanol and the obtained crystals are heated in 20% sodium hydroxide solution for 2 hours. After addition of ethanol the solution is filtered, acidified with glacial acetic acid and the crystals are removed by suction filtration. The hydrochloride (yellow crystals) is obtained from the free base by acidifying with hydrochloric acid.

Analysis: $C_{17}H_{10}N_2O_3 \cdot HCl$

	C%	H%	N%	Cl%
calc:	62.48	3.37	8.58	10.87
found:	62.62	3.50	8.33	10.02

Example 6.

11 - Oxo - 11 - H - 2 - methoxy - pyrido-[2,1 - b] - quinazoline - 8 - carboxylic acid



1.58 g of 6-chloronicotinic acid are heated with 3.9 g of ethyl 5-methoxyanthranilate to 160°C and processed as described in Example 5. The compound is isolated as the hydrochloride and melts above 300°C.

Analysis: $C_{14}H_{10}N_2O_4 \cdot HCl$

	C%	H%	N%	Cl%
calc:	54.81	3.59	9.14	11.58
found:	54.78	3.66	8.94	11.56

The following compounds are obtained by processes analogous to Examples 1 to 6:—

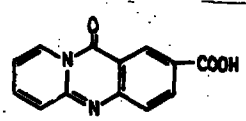
6 - oxo - 6 - H - pyrimido[2,1 - b] - quinazoline - 8 - carboxylic acid,

12 - oxo - 12 - H - quino[2,1 - b] - quinazoline - 10 - carboxylic acid,

11 - oxo - 11 - H - pyrido[2,1 - b] - quinazoline - 3 - carboxylic acid.

Example 7.

11 - Oxo - 11 - H - pyrido[2,1 - b] - quinazoline - 2 - carboxylic acid



Molar quantities of 2,4-dimethylaniline and 2-bromopyridine are condensed at 160 to 180°C and 2,4 - dimethyl - N - pyridyl - (2)-aniline (having a melting point after purification *via* the fumarate of 65 to 68°C) is obtained. Heating it with acetic anhydride gives N - pyridyl(2) - N - 2,4 - dimethylphenyl-acetamide. 60 g of this acetamide are oxidized with 218 g of potassium permanganate and

75.5 g of magnesium sulfate in 2 l of water between 40 and 90°C.

The manganese dioxide produced is removed by suction filtration and the mother liquor acidified with acetic acid. The compound that crystallises out slowly is removed by suction filtration.

After stirring for one hour with 5 times its quantity of concentrated hydrochloric acid at 60 to 70°C, it is diluted with 10 times its quantity of water. The 11 - oxo - 11 - H-pyrido[2,1 - b] - quinazoline - 2 - carboxylic acid precipitates gradually, and after removal is washed with water and acetonitrile.

Analysis: $C_{13}H_8H_2O_8$

	C%	H%	N%
calc:	65.00	3.33	11.67
found:	64.95	3.46	11.58

a) *Sodium Salt*
From the obtained pyrido-quinazolone carboxylic acid, the sodium salt is obtained in water with the calculated quantity of sodium bicarbonate and subsequently precipitated with ethanol.

b) *Ethanolamine Salt*
1.2 g of the obtained pyrido-quinazolone-carboxylic acid are suspended in 3 ml of water, 0.31 ml of ethanolamine are added and the ethanolamine salt is precipitated with acetonitrile.

Analysis: $C_{15}H_{15}N_3O_4 . H_2O$

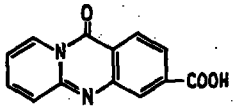
	C%	H%	N%
calc:	56.43	5.33	13.17
found:	57.25	4.96	13.46

c) *Triethanolamine Salt*
From 2.4 g of pyrido-quinazolone carboxylic acid suspended in 200 ml of acetonitrile, the above salt is produced with 3.6 g of triethanolamine (approx. 85%). (decomposition >200°C)

Analysis: $C_{19}H_{23}N_3O_8$

	C%	H%	N%
calc:	58.61	5.91	10.80
found:	58.80	5.72	11.00

Example 8.
11 - Oxo - 11 - H - pyrido[2,1 - b]-quinazoline - 3 - carboxylic acid

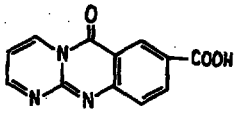


Analogous to Example 7, 2,5-dimethylaniline and 2-bromopyridine are reacted *via* the N - pyridyl(2) - N - (2,5 - dimethylphenyl)acetamide and oxidation with potassium permanganate to 11 - oxo - 11 - H-pyrido[2,1 - b] - quinazoline - 3 - carboxylic acid.

Analysis: $C_{13}H_8N_2O_3$

	C%	H%	N%
calc:	65.50	3.33	11.67
found:	65.24	3.21	11.79

Example 9.
6 - Oxo - 6 - H - pyrimido[2,1 - b]-quinazoline - 8 - carboxylic acid



9.5 g of 2-aminopyrimidine are heated with 18.5 g of 4-bromo-*m*-xylene, 13.8 g of potassium carbonate and 0.5 g of copper powder to 180°C for 5 hours. The reaction mixture is then diluted with water, extracted with ether and after evaporating the solvent, 2.4 - dimethyl - N - pyrimidyl(2) - aniline (m.p. 95—99°C) is isolated.

As described in Example 7 for the analogous pyridyl compound, it is acetylated, oxidized with potassium permanganate, cyclized and the 6 - oxo - 6 - H - pyrimido-[2,1 - b] - quinazoline - 8 - carboxylic acid hydrochloride is obtained.

Analysis: $C_{12}H_7N_3O_3 . HCl$

	C%	H%	N%
calc:	51.89	2.88	15.33
found:	51.89	3.03	15.87

From the hydrochloride, the sodium salt is obtained in water with 2 mol of sodium bicarbonate and pricipitating with ethanol.

Analogously to Examples 7 to 9, 11 - oxo-11 - H - 2 - methoxypyrido[2,1 - b] - quinazoline - 8 - carboxylic acid (which may be converted into its salts) may be obtained.

Example 10.
8 - Acetamido - 11 - H - 11 - oxo - pyrido-[2,1 - b] - quinazoline - 2 - carboxylic acid

By reacting 23.8 g of 2-chloro-5-nitropyridine with 19 g of 2,4-dimethylaniline at 160°C, 2,4 - dimethyl - N - 5 - nitropyridyl-(2) - aniline is obtained, from which after reduction with 76 g of tin-(II)-chloride and acetylating with 210 ml of acetic anhydride, N - (5 - diacetylaminopyridyl - (2)) - N-(2,4 - dimethylphenyl)acetamide is obtained. 9.5 g of this compound are stirred with 26.5 g of potassium permanganate and 3.5 g of mag-

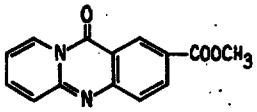
nesium sulfate in a water-butanol mixture (2:1) for 4 hours at 80 to 85°C. After suction filtration and evaporating, the residue is heated with dilute acetic acid for 1 hour, whereby 8 - acetamido - 11 - H - 11 - oxo-pyrido - [2,1 - b] - quinazoline - 2 - carboxylic acid gradually crystallises out. It is removed by suction filtration and washed with acetonitrile and ether.

Analysis: $C_{16}H_{11}N_3O_4 . H_2O$

	C%	H%	N%	H_2O%
calc:	57.14	4.76	13.33	5.7
found:	57.68	4.69	13.15	4.1

Example 11.

Methyl 11 - Oxo - 11 - H - pyrido[2,1 - b] - quinazoline - 2 - carboxylate



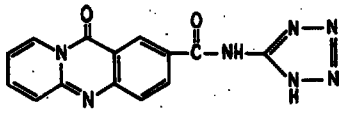
6.2 g of the 11 - oxo - 11 - H - pyrido[2,1-b] - quinazoline - 2 - carboxylic acid produced in Example 7 are refluxed in ten times its quantity of thionyl chloride for 1 hour. The insoluble carboxylic acid chloride is sucked off and refluxed in 10 to 20 times its quantity of methanol until complete solution. After cooling, the methyl 11 - oxo - 11 - H - pyrido-[2,1 - b] - quinazoline - 2 - carboxylate hydrochloride crystallizes out with one mol. of methanol (decomposition point 254°C).

Analysis: $C_{14}H_{10}N_2O_3 . HCl . CH_3OH$

	C%	H%	N%	Cl%
calc:	55.81	4.65	8.68	11.01
found:	55.53	4.35	8.82	11.29

Example 12.

11 - Oxo - 11 - H - pyrido[2,1 - b] - N - (1-H - tetrazol - 5 - yl) - quinazoline - 2-carboxamide



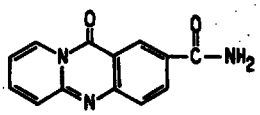
5.53 g of the 11 - oxo - 11 - H - pyrido-[2,1 - b] - quinazoline - 2 - carboxylic acid chloride hydrochloride produced as in Example 11 are dissolved with 2.1 g of aminotetrazole hydrate, 6.1 g of triethylamine and 200 ml of dimethylformamide at 0 to 10°C and stirred for 3 hours. Afterwards acetic acid is added to the reaction mixture until acid and the product removed by suction filtration (decomposition point 330°C).

Analysis: $C_{14}H_9N_7O_2$

	C%	H%	N%
calc:	54.72	2.93	31.92
found:	54.93	3.17	31.63

Example 13.

11 - Oxo - 11 - H - pyrido[2,1 - b] - quinazoline - 2 - carboxamide



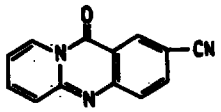
As in Example 11, the carboxylic acid chloride is produced from 10 g of 11 - oxo-11 - H - pyrido[2,1 - b] - quinazoline - 2-carboxylic acid. It is then stirred in a mixture of 200 ml of dioxan and 50 ml of conc. ammonia for 5 hours at room temperature. Afterwards, dilute acetic acid is added to the reaction mixture until acid and the crystals removed by suction filtration.

Analysis: $C_{18}H_9N_3O_2$

	C%	H%	N%
calc:	65.27	3.77	17.57
found:	65.00	3.65	17.38

Example 14.

2 - Cyano - 11 - oxo - 11 - H - pyrido-[2,1 - b] - quinazoline



4.8 g of 11 - oxo - 11 - H - pyrido[2,1-b] - quinazoline - 2 - carboxamide (Example 13) are suspended in 150 ml of dimethylformamide and 3.3 ml of thionyl chloride are added dropwise. When the addition is complete the reaction mixture is stirred at 90 to 110°C for 10 hours. It is then neutralized with dilute sodium carbonate solution and suction filtered.

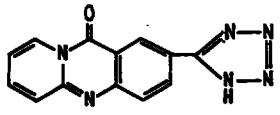
By recrystallization from dimethylformamide, 2 - cyano - 11 - oxo - 11 - H - pyrido-[2,1 - b] - quinazoline is obtained (decomposition 268—271°C).

Analysis: $C_{18}H_7N_3O$

	C%	H%	N%
calc:	70.59	3.17	19.00
found:	70.42	3.04	19.00

Example 15.

11 - Oxo - 11 - H - pyrido[2,1 - b] - 2-(1H - tetrazol - 5 - yl) - quinazoline



5.2 g of 2 - cyano - 11 - oxo - 11 - H-pyrido[2,1 - b] - quinazoline (Example 14), 1.8 g of sodium azide and 1.5 g of ammonium chloride are heated in 60 ml of dimethylformamide for 10 hours to 90 to 110°C.

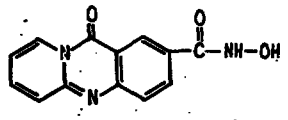
The mixture is acidified with dilute acetic acid and the tetrazolylquinazoline product is removed by suction filtration.

Analysis: $C_{13}H_8N_6O$

	C%	H%	N%
calc:	59.09	3.03	31.82
found:	58.88	3.26	31.96

Example 16.

11 - Oxo - 11 - H - pyrido[2,1 - b]-quinazoline - 2 - hydroxamic acid



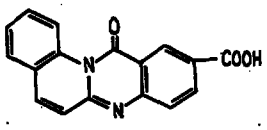
5.9 g of 11 - oxo - 11 - H - pyrido[2,1-b] - quinazoline - 2 - carboxylic acid chloride hydrochloride produced according to Example 11 are dissolved in 2.08 g of hydroxylamine hydrochloride, 0.8 ml of diisopropylamine and 100 ml of dimethyl formamide at 20°C and stirred for 5 hours. After acidification with dilute acetic acid the product is removed by suction filtration.

Analysis: $C_{13}H_9N_3O_3 \cdot 1/2\ H_2O$

	C%	H%	N%
calc:	59.09	3.79	15.91
found:	59.20	3.70	15.49

Example 17.

12 - Oxo - 12 - H - quino[2,1 - b] - quinazoline - 10 - carboxylic acid



2.8 g of ethyl 12 - oxo - 12 - H - quino-[2,1 - b] - quinazoline - 10 - carboxylate, produced as described in Example 3, are refluxed in 20 ml of 10% sodium hydroxide solution for 30 minutes. The solution is heated with 5 times its quantity of semi-concentrated hydrochloric acid for half an hour in a boiling water-bath. After diluting with water the precipitated yellow crystals are removed by suction filtration and washed with water and acetonitrile.

Analysis: $C_{17}H_{10}N_2O_3$

	C%	H%	N%	O%
calc:	70.34	3.45	9.66	16.55
found:	70.23	3.50	9.53	17.02

Analogously with Examples 11 to 17, the following compounds are obtained:—

Ethyl - 5 - oxo - 5 - H - thiazolo[2,3 - b]-quinazoline - 7 - carboxylate;
Ethyl 8 - oxo - 8 - H - isoquino[1,2 - b]-quinazoline - 10 - carboxylate;
Ethyl 12 - oxo - 12 - H - quino[2,1 - b]-quinazoline - 10 - carboxylate;
11 - oxo - 11 - H - 2 - methyl - pyrido[2,1-b] - quinazoline - 8 - carboxylic acid;
13 - oxo - 13 - H - benzo[g] - pyrido[2,1-b] - quinazoline - 10 - carboxylic acid;
11 - oxo - 11 - H - 2 - methoxy - pyrido-[2,1 - b] - quinazoline - 8 - carboxylic acid;
11 - oxo - 11 - H - pyrido[2,1 - b] - quinazoline - 3 - carboxylic acid;
6 - oxo - 6 - H - pyrimido[2,1 - b] - quinazoline - 8 - carboxylic acid;
5 - oxo - 5 - H - thiazolo[2,3 - b] - quinazoline - 7 - carboxylic acid;
8 - oxo - 8 - H - isoquino[1,2 - b] - quinazoline - 10 - carboxylic acid;
11 - oxo - 11 - H - pyrido[2,1 - b] - quinazoline - 2,8 - dicarboxylic acid.

The above compounds may also be isolated as their acid addition salts preferably with strong acids. These containing a carboxyl group may also be converted into the corresponding basic addition salts e.g. with alkalis or with alkyl amines.

Example 18.

8 - Amino - 11 - H - 11 - oxopyrido - [2,1-b] - quinazoline - 2 - carboxylic acid

3.4 g of 8 - acetamido - 11 - H - 11 - oxo-pyrido - [2,1 - b] - 2 - carboxylic acid produced as in Example 10 are heated in a boiling water-bath with 30 ml of a mixture of water with concentrated sulfuric acid (2:3) for 30 minutes. The reaction mixture is diluted with water, cooled and suction filtered. The 8 - amino - 11 - H - 11 - oxopyrido-[2,1 - b] - quinazoline - 2 - carboxylic acid thus obtained is purified by dissolving in soda solution, precipitated with glacial acetic acid, suction filtered and washed with acetonitrile and ether.

Analysis: $C_{13}H_9N_3O_3 \cdot H_2O$

	C%	H%	N%	H_2O%
calc:	57.14	4.03	15.38	6.6
found:	56.95	4.09	15.29	7.1

Example I: Tablets

Composition:

a) 11-oxo-11-H-pyrido[2,1-b]-quinazoline-2-carboxylic acid	0.100 g

stearic acid	0.020 g
glucose	1.890 g
	2.000 g

b) active ingredient according to

the invention	0.200 g
stearic acid	0.020 g
glucose	1.780 g
	2.000 g

The components are processed in the conventional way to produce tablets of the composition indicated above.

Example II: Ointments

Composition:	g/100 g ointment
active ingredient acc. to invention	2.000
fuming hydrochloric acid	0.011
sodium pyrosulfite	0.050
mixture of equal parts of cetal alcohol and stearyl alcohol	20.000
white vaseline	5.000
artificial Bergamotte oil	0.075
distilled water	ad 100.00

The components are processed to produce an ointment in the usual way.

Example III: Inhalation Aerosol

Composition:	parts
sodium salt of 11-oxo-11-H-pyrido-[2,1-b]-quinazoline-2-carboxylic acid	1.00
soja lecithin	0.20
propellant gas mixture (Frigene 11, 12 and 114)	ad 100.00

The preparation is filled into aerosol containers with metering means in such a way that a dose of 5 mg of active ingredient is released. For higher doses preparations with a higher content of active ingredient are used.

Example IV: Ampoules (Injection Solutions)

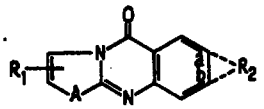
Composition:	Parts by weight
13-oxo-13-H-benzo[g]-pyrido-[2,1-b]-quinazoline-10-carboxylic acid	10.0
sodium pyrosulfite	1.0
disodium salt of ethylene diamine-tetraacetic acid	0.5
sodium chloride	8.5
doubly distilled water	at 100.00

The active ingredient and excipients are dissolved in a sufficient quantity of water and brought to the desired concentration with the required quantity of water.

The solution is filtered and filled into 1 ml ampoules under aseptic conditions. The ampoules are sterilized and sealed. Each ampoule contains 10 mg of active ingredient.

WHAT WE CLAIM IS:—

1. Compounds of general formula



(I)

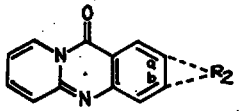
[wherein A represents a group of the formula

—CH=CH—, —CH=N— or —S—;

R_1 represents a hydrogen atom, an alkyl or akloxy group each containing from 1 to 4 carbon atoms, an amino or acetylamino group, a fused benzene ring, a cyano or tetrazol-5-yl group or a group of the formula —COR_3 (wherein R_3 represents an alkoxy group containing from 1 to 4 carbon atoms, an amino, hydroxylamino or tetrazol-5-yl-amino group or where R_2 as hereinafter defined is other than a hydrogen atom, can additionally represent a hydroxy group); and

R_2 represents a cyano or tetrazol-5-yl group, a group of the formula —COR_4 (wherein R_4 represents an alkoxy group containing from 1 to 4 carbon atoms, a hydroxy, amino, hydroxylamino or tetrazol-5-yl-amino group) or, when R_1 represents a cyano or tetrazol-5-yl group or group of the formula —COR_3 as defined above, can additionally represent a hydrogen atom, an alkyl or alkoxy group each containing from 1 to 4 carbon atoms, an amino or acetylamino group or a fused benzene ring, with the proviso that when A is a group of formula —CH=CH— and R_1 is a hydrogen atom or an alkyl, alkoxy, cyano or tetrazol-5-yl group or a group of the formula —COR_3, then R_2 is other than a hydrogen atom or a cyano, tetrazol-5-yl, alkyl, alkoxy, amino or acetylamino group or a group of the formula —COR_4; and the dotted lines in formula I indicating that R_2 is attached to the *a*- or *b*-positions, where R_2 is other than a fused benzene ring] and the salts thereof.

2. Compounds of general formula



(Ia)

(wherein R_2 represents a carboxyl, methoxycarbonyl, tetrazol-5-yl-carbamoyl or cyano group; and the dotted lines indicate that R_2 is attached at the *a* or *b* positions) and salts thereof.

3. Compounds of general formula I as

stearic acid	0.020 g
glucose	1.890 g
	2.000 g

b) active ingredient according to the invention 0.200 g
stearic acid 0.020 g
glucose 1.780 g
2.000 g

The components are processed in the conventional way to produce tablets of the composition indicated above.

Example II: Ointments

Composition:	g/100 g ointment
active ingredient acc. to invention	2.000
fuming hydrochloric acid	0.011
sodium pyrosulfite	0.050
mixture of equal parts of cetal alcohol and stearyl alcohol	20.000
white vaseline	5.000
artificial Bergamotte oil	0.075
distilled water	ad 100.00

The components are processed to produce an ointment in the usual way.

Example III: Inhalation Aerosol

Composition:	parts
sodium salt of 11-oxo-11-H-pyrido-[2,1-b]-quinazoline-2-carboxylic acid	1.00
soja lecithin	0.20
propellant gas mixture (Frigene 11, 12 and 114)	ad 100.00

The preparation is filled into aerosol containers with metering means in such a way that a dose of 5 mg of active ingredient is released. For higher doses preparations with a higher content of active ingredient are used.

Example IV: Ampoules (Injection Solutions)

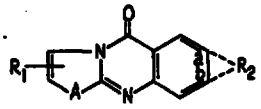
Composition:	Parts by weight
13-oxo-13-H-benzo[g]-pyrido-[2,1-b]-quinazoline-10-carboxylic acid	10.0
sodium pyrosulfite	1.0
disodium salt of ethylene diamine-tetraacetic acid	0.5
sodium chloride	8.5
doubly distilled water	at 100.00

The active ingredient and excipients are dissolved in a sufficient quantity of water and brought to the desired concentration with the required quantity of water.

The solution is filtered and filled into 1 ml ampoules under aseptic conditions. The ampoules are sterilized and sealed. Each ampoule contains 10 mg of active ingredient.

WHAT WE CLAIM IS:—

1. Compounds of general formula



(I)

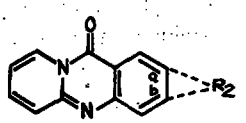
[wherein A represents a group of the formula

—CH=CH—, —CH=N— or —S—;

R_1 represents a hydrogen atom, an alkyl or akloxy group each containing from 1 to 4 carbon atoms, an amino or acetylamino group, a fused benzene ring, a cyano or tetrazol-5-yl group or a group of the formula —COR_3 (wherein R_3 represents an alkoxy group containing from 1 to 4 carbon atoms, an amino, hydroxylamino or tetrazol-5-yl-amino group or where R_2 as hereinafter defined is other than a hydrogen atom, can additionally represent a hydroxy group); and

R_2 represents a cyano or tetrazol-5-yl group, a group of the formula —COR_4 (wherein R_4 represents an alkoxy group containing from 1 to 4 carbon atoms, a hydroxy, amino, hydroxylamino or tetrazol-5-yl-amino group) or, when R_1 represents a cyano or tetrazol-5-yl group or group of the formula —COR_3 as defined above, can additionally represent a hydrogen atom, an alkyl or alkoxy group each containing from 1 to 4 carbon atoms, an amino or acetylamino group or a fused benzene ring, with the proviso that when A is a group of formula —CH=CH— and R_1 is a hydrogen atom or an alkyl, alkoxy, cyano or tetrazol-5-yl group or a group of the formula —COR_3, then R_2 is other than a hydrogen atom or a cyano, tetrazol-5-yl, alkyl, alkoxy, amino or acetylamino group or a group of the formula —COR_4; and the dotted lines in formula I indicating that R_2 is attached to the *a*- or *b*-positions, where R_2 is other than a fused benzene ring] and the salts thereof.

2. Compounds of general formula



(Ia)

(wherein R_2 represents a carboxyl, methoxycarbonyl, tetrazol-5-yl-carbamoyl or cyano group; and the dotted lines indicate that R_2 is attached at the *a* or *b* positions) and salts thereof.

3. Compounds of general formula I as

claimed in claim 1 [wherein A represents a group of the formula —CH=CH— or —S—;

R_1 represents a hydrogen atom, a fused benzene ring, a tetrazol-5-yl group or a group of the formula —COR_3 (wherein R_3 represents a hydroxylamino or tetrazol-5-yl-amino group or, where R_2 as hereinafter defined is other than a hydrogen atom, can additionally represent a hydroxy group); and

R_2 represents a tetrazol-5-yl group, a group of the formula —COR_4 (wherein R_4 represents a hydroxy, hydroxylamino or tetrazol-5-yl-amino group) or, when R_1 represents a tetrazol-5-yl group or group of the formula —COR_3 as defined above, can additionally represent a hydrogen atom or a fused benzene ring] and the salts thereof.

4. 11 - Oxo - 11 - H - pyrido[2,1 - b]-quinazoline - 2 - carboxylic acid and the salts thereof.

5. Ethyl 5 - oxo - 5 - H - thiazolo[2,3 - b]-quinazoline - 7 - carboxylate and the salts thereof.

6. 13 - Oxo - 13 - H - benzo[g] - pyrido-[2,1 - b] - quinazoline - 10 - carboxylic acid and the salts thereof.

7. 11 - Oxo - 11 - H - pyrido[2,1 - b]-quinazoline - 3 - carboxylic acid and the salts thereof.

8. Methyl 11 - oxo - 11 - H - pyrido[2,1-b] - quinazoline - 2 - carboxylate and the salts thereof.

9. 11 - Oxo - 11 - H - pyrido[2,1 - b]-N - (1 - H - tetrazol - 5 - yl) - quinazoline-2 - carboxamide and the salts thereof.

10. 2 - Cyano - 11 - oxo - 11 - H - pyrido-[2,1 - b] - quinazoline and the salts thereof.

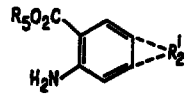
11. Compounds as claimed in either of claims 1 and 2 as herein specifically disclosed, with the exception of the compounds claimed in any of claims 4 to 10.

12. A process for the preparation of compounds as claimed in either of claims 1 and 2 (wherein R_1 represents a hydrogen atom, an alkyl or alkoxy group each containing from 1 to 4 carbon atoms, an acetylamino group, a fused benzene ring, or a tetrazol-5-yl or carboxyl group, and R_2 represents a tetrazol-5-yl or carboxyl group or, when R_1 represents a tetrazol-5-yl or carboxyl group, R_2 can additionally represent an alkyl or alkoxy group each containing from 1 to 4 carbon atoms, an acetylamino group or a fused benzene ring) which comprises reacting a compound of formula



(II)

(wherein A is as defined in claim 1; R_1' represents a hydrogen atom, an alkyl or alkoxy group each containing from 1 to 4 carbon atoms, an acetylamino group, a fused benzene ring, or a tetrazol-5-yl or carboxyl group; and X represents a halogen atom) with a compound of formula



(III)

(wherein R_2' represents a tetrazol-5-yl or carboxyl group, an alkoxycarbonyl group containing from 1 to 4 carbon atoms in the alkoxy moiety thereof, or when R_1' represents a tetrazol-5-yl or carboxyl group, can additionally represent an alkyl or alkoxy group each containing from 1 to 4 carbon atoms, an acetylamino group or a fused benzene ring, with the proviso that when A in the compound of formula II represents a group of formula —CH=CH—, and R_1' in the compound of formula II represents a hydrogen atom or an alkyl, alkoxy, tetrazol-5-yl, or carboxyl group, then R_2' is other than a tertazol-5-yl, alkyl, alkoxy or acetylamino group or an alkoxycarbonyl group having from 2 to 4 carbon atoms in the alkyl moiety thereof; and R_5 represents a hydrogen atom or an alkyl group containing from 1 to 4 carbon atoms).

13. A process as claimed in claim 12 wherein the reaction is effected at an elevated temperature.

14. A process as claimed in claim 13 wherein the reaction is effected at a temperature of 120 to 160°C.

15. A process as claimed in any of claims 12 to 14 wherein a compound of formula II is used in which X represents a fluorine, chlorine or bromine atom.

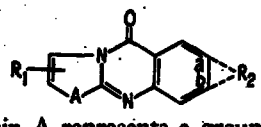
16. A process as claimed in any of claims 12 to 15 wherein the reaction is effected in the presence of a high boiling solvent.

17. A process as claimed in claim 16 wherein the high boiling solvent comprises dimethylformamide or sulfolane.

18. A process as claimed in any of claims 12 to 17 wherein the reaction is effected in the presence of an acid-acceptor.

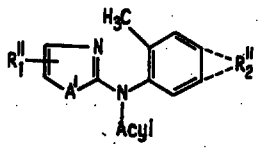
19. A process as claimed in claim 18 wherein the acid-acceptor comprises an excess of the compound of formula III.

20. A process for the preparation of compounds of general formula



(I)

(wherein A represents a group of the formula —CH=CH— or —CH=N—; R_1 represents a hydrogen atom, an alkoxy group containing from 1 to 4 carbon atoms or a carboxyl group; and R_2 represents a carboxyl group, or when R_1 represents a carboxyl group, can additionally represent an alkoxy group containing from 1 to 4 carbon atoms; and the dotted line is as defined in claim 1) which comprises oxidising a compound of formula



(IV)

(wherein A' represents a group of the formula —CH=CH— or —CH=N—, R_1'' represents a hydrogen atom, an alkoxy group containing from 1 to 4 carbon atoms or a carboxyl group; and R_2'' represents a methyl or a carboxyl group or, when R_1 represents a carboxyl group, can additionally represent an alkoxy group containing from 1 to 4 carbon atoms) and subsequently acidifying the compound thereby formed.

21. A process as claimed in claim 20 wherein the oxidation is effected at an elevated temperature.

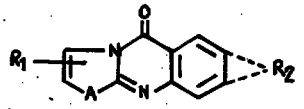
22. A process as claimed in either of claims 20 and 21 wherein the oxidation is effected with an aqueous solution of potassium permanganate buffered with magnesium sulphate.

23. A process as claimed in any of claims 20 to 22 wherein the acidification is effected with a mineral or organic acid.

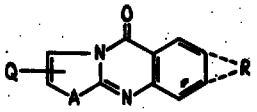
24. A process as claimed in claim 23 wherein the acid comprises hydrochloric acid.

25. A process as claimed in claim 23 wherein the acid comprises acetic acid.

26. A process for the preparation of compounds of general formula



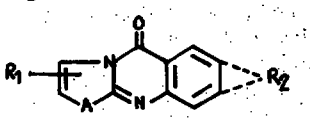
(wherein R_1 and R_2 are as defined in claim 1 except that the proviso therein does not apply, and wherein at least one of R_1 and R_2 represents a carbamoyl or N - (tetrazol - 5 - yl)-carbamoyl group and A and the dotted line are as defined in claim 1) wherein a compound of formula



(V)

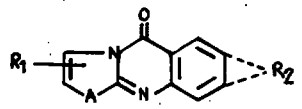
(wherein Q and/or R represent chlorocarbonyl groups) is reacted with ammonia or aminotetrazole.

27. A process for the preparation of compounds of general formula



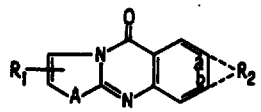
(wherein R_1 and R_2 are as defined in claim 1 except that the proviso therein does not apply, and wherein at least one of R_1 and R_2 represents an N-hydroxyl-carbamoyl group, and A and the dotted lines are as defined in claim 1) wherein a compound of formula V as defined in claim 26 is reacted with hydroxylamine.

28. A process for the preparation of compounds of general formula



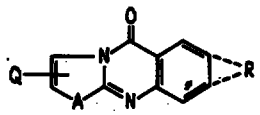
(wherein R_1 and R_2 are as defined in claim 1 except that the proviso therein does not apply, and wherein at least one of R_1 and R_2 represents an ester group, and A and the dotted lines are as defined in claim 1) wherein a compound of formula V as defined in claim 26 is reacted with an aliphatic alcohol containing from 1 to 4 carbon atoms.

29. A process for the preparation of compounds of general formula



(I)

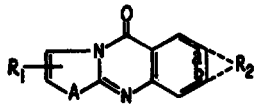
(wherein R_1 and R_2 are as defined in claim 1 except that the proviso therein does not apply, and wherein at least one of R_1 and R_2 represents a tetrazol-5-yl group, and A and the dotted lines are as defined in claim 1) wherein a compound of formula



(V)

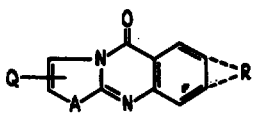
(wherein Q and/or R represent cyano groups) is reacted with sodium azide.

30. A process for the preparation of compounds of general formula



(I)

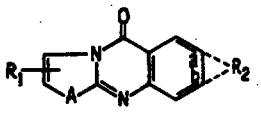
(wherein R_1 and R_2 are as defined in claim 1 except that the proviso therein does not apply, and wherein at least one of R_1 and R_2 represents a cyano group, and A and the dotted lines are as defined in claim 1) wherein a compound of formula



(V)

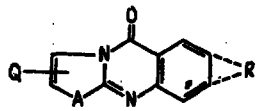
(wherein Q and/or R represent carbamoyl groups) is dehydrated.

31. A process for the preparation of compounds of general formula



(I)

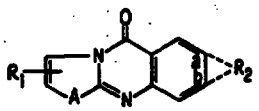
(wherein R_1 and R_2 are as defined in claim 1 except that the proviso therein does not apply, and wherein at least one of R_1 and R_2 represents a carboxyl group, and A and the dotted lines are as defined in claim 1) wherein a compound of formula



(V)

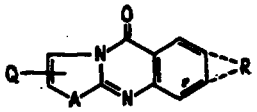
(wherein Q and/or R represent ester or amido groups) is saponified.

32. A process for the preparation of compounds of general formula



(I)

(wherein R_1 and R_2 are as defined in claim 1 except that the proviso therein does not apply, and wherein at least one of R_1 and R_2 represents a carboxyl group, and A and the dotted lines are as defined in claim 1) wherein a compound of formula

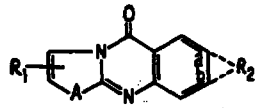


(V)

(wherein Q and/or R represent methyl groups) is oxidised.

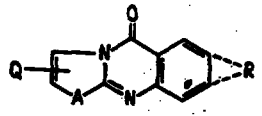
33. A process as claimed in claim 32 wherein the oxidation is effected with potassium permanganate.

34. A process for the preparation of compounds of general formula



(I)

(wherein R_1 and R_2 are as defined in claim 1 except that the proviso therein does not apply, and wherein at least one of R_1 and R_2 represents an amino group, and A and the dotted lines are as defined in claim 1) wherein a compound of formula



(V)

(wherein Q or R represents an acylamino group) is subjected to acid or alkaline saponification.

35. A process as claimed in any of claims 12 to 34 wherein the compound produced is converted to an acid addition salt thereof or, when R_1 and/or R_2 in the compound produced represents carboxyl groups, to a salt thereof with an organic or inorganic base.

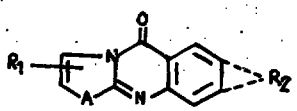
36. A process for the preparation of compounds of general formula I and the salts thereof substantially as herein described.

37. A process for the preparation of compounds substantially as herein described in any one of Examples 1 to 18.

38. Compounds whenever prepared by a process as claimed in any of claims 12 to 37.

39. Pharmaceutical compositions comprising, as active ingredient, a compound of formula I or Ia as defined in claim 1 or claim 2 or a physiologically acceptable salt thereof in association with a pharmaceutical carrier or excipient.

40. Pharmaceutical compositions comprising as active ingredient a compound of formula



(wherein A, R_1, R_2 and the dotted lines are as defined in claim 1 except that the proviso therein does not apply) or a physiologically acceptable acid addition salt thereof, in association with a pharmaceutical carrier or excipient, in a form suitable for oral, rectal, parenteral, pulmonary or topical administration.

41. Compositions as claimed in either of claims 39 and 40 in the form of capsules, tablets, coated tablets, solutions, suspensions, aerosols, sterile isotonic solutions, creams, ointments, lotions, emulsions, sprays or suppositories.

42. Compositions as claimed in any of claims 39 to 41 in dosage unit form.

43. Compositions as claimed in claim 42 for pulmonary administration wherein each dosage unit comprises from 20 to 500μg/kg of the said active ingredient.

44. Compositions as claimed in claim 42 for oral administration wherein each dosage unit comprises 1 to 50 mg of the said active ingredient.

45. Compositions as claimed in claim 42 for intravenous administration wherein each dosage unit comprises 0.2 to 10 mg of the said active ingredient.

46. Compositions as claimed in claim 42 for nasal or ocular administration wherein each dosage unit comprises from 0.5 to 25 mg of the said active ingredient.

47. Pharmaceutical compositions as claimed in any one of claims 39 to 46 substantially as herein described.

48. Pharmaceutical compositions substantially as herein described in any one of Examples I to IV.

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