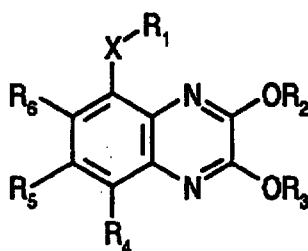


Novel quinoxaline- and quinoxalinylalkane-phosphonic acids

The invention relates to novel quinoxaline- and quinoxalinylalkane-phosphonic acids of formula I



(I),

wherein

R₁ is free or partially esterified phosphono,

R₂ and R₃ are each independently of the other hydrogen or an aliphatic radical,

the radicals R₄, R₅ and R₆ are each independently of the others hydrogen, an aliphatic hydrocarbon radical, free or etherified hydroxy, free or etherified mercapto or oxidised free or etherified mercapto, unsubstituted or aliphatically substituted amino, nitro, free or esterified or amidated carboxy, cyano, free or amidated sulfamoyl, halogen or trifluoromethyl, and

X is a divalent aliphatic radical,

and

to the tautomers and/or salts thereof, to pharmaceutical compositions comprising the novel compounds and to the use thereof as active ingredients of medicaments.

Free or esterified carboxy is, for example, carboxy, lower alkoxycarbonyl, or phenyl-lower alkoxycarbonyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl.

Free or partially esterified phosphono is, for example, lower alkylphosphono.

Aliphatic radicals R_1 and/or R_2 are, for example, lower alkyl, lower alkenyl or lower alkynyl radicals; groups R_1O and R_2O are, for example, hydroxy or lower alkoxy, but may also be lower alkenyloxy or lower alkynyloxy.

Aliphatic hydrocarbon radicals are, for example, lower alkyl or lower alkenyl radicals, but may also be lower alkynyl radicals.

Free or etherified mercapto or oxidised free or etherified mercapto, is, for example, mercapto, lower alkylthio, lower alkanesulfinyl or lower alkanesulfonyl, but may also be lower alkenylthio, lower alkynylthio, lower alkenesulfinyl, lower alkenesulfonyl, lower alkynesulfinyl or lower alkynesulfonyl.

Unsubstituted or aliphatically substituted amino is, for example, amino or N-mono- or N,N-di-lower alkylamino.

Free or esterified or amidated carboxy is, for example, carboxy, lower alkoxycarbonyl; phenyl-lower alkoxycarbonyl that is unsubstituted or substituted by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; carbamoyl, N-mono- or N,N-di-lower alkyl-carbamoyl, or N-phenylcarbamoyl or N-phenyl-N-lower alkyl-carbamoyl each of which is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl.

Free or amidated sulfamoyl is, for example, sulfamoyl or N-mono- or N,N-di-lower alkyl-sulfamoyl.

Halogen is, for example, halogen having an atomic number of up to and including 35, such as fluorine, chlorine or bromine.

Divalent aliphatic radicals are, for example, lower alkylidene, lower alkylene, lower alkenylene or lower alkynylene radicals.

Hereinbefore and hereinafter, "lower" radicals and compounds are to be understood as being, for example, radicals and compounds having up to and including 7, preferably up to and including 4, carbon atoms.

Di-lower alkylamino is, for example, di-C₁-C₄alkylamino, such as dimethylamino, diethylamino, dipropylamino, diisopropylamino or dibutylamino.

Di-lower alkylcarbamoyl is, for example, di-C₁-C₄alkylcarbamoyl, such as dimethylcarbamoyl, diethylcarbamoyl, dipropylcarbamoyl, diisopropylcarbamoyl or dibutylcarbamoyl.

Di-lower alkylsulfamoyl is, for example, di-C₁-C₄alkylsulfamoyl, such as dimethylsulfamoyl, diethylsulfamoyl, dipropylsulfamoyl, diisopropylsulfamoyl or dibutylsulfamoyl.

Lower alkoxy carbonyl is, for example, C₁-C₇alkoxy carbonyl, preferably C₁-C₄alkoxy carbonyl, such as methoxy carbonyl, ethoxy carbonyl, propyloxy carbonyl, isopropyloxy carbonyl or butyloxy carbonyl, but may also be isobutyloxy carbonyl, secondary butyloxy carbonyl, tertiary butyloxy carbonyl or a pentyloxy carbonyl, hexyloxy carbonyl or heptyloxy carbonyl group.

Lower alkanesulfinyl is, for example, C₁-C₇alkanesulfinyl, preferably C₁-C₄alkanesulfinyl, such as methanesulfinyl, ethanesulfinyl, propanesulfinyl or butanesulfinyl, but may also be a pentanesulfinyl, hexanesulfinyl or heptanesulfinyl group.

Lower alkanesulfonyl is, for example, C₁-C₇alkanesulfonyl, preferably C₁-C₄alkanesulfonyl, such as methanesulfonyl, ethanesulfonyl, propanesulfonyl or butanesulfonyl, but may also be a pentanesulfonyl, hexanesulfonyl or heptanesulfonyl group.

Lower alkenesulfinyl is, for example, C₃-C₄alkenesulfinyl, such as prop-2-enesulfinyl or but-2-enesulfinyl.

Lower alkenesulfonyl is, for example, C₃-C₄alkenesulfonyl, such as prop-2-enesulfonyl or but-2-enesulfonyl.

Lower alkenyl is, for example, C₃-C₄alkenyl, such as allyl or methallyl.

Lower alkenylene may be straight-chained or branched and may be bonded in any desired position and is, for example, straight-chained or branched C₂-C₇alkenylene, especially C₂-C₄alkylene, such as vinylene, 1,3-prop-2-enylene or 1,4-but-2-enylene.

Lower alkenyloxy is, for example, C₃-C₄alkenyloxy, such as allyloxy or methallyloxy.

Lower alkynyl is, for example, C₃-C₄alkynyl, such as propargyl.

Lower alkynyloxy is, for example, C₃-C₄alkynyloxy, such as propargyloxy.

Lower alkynylthio is, for example, C₃-C₄alkynylthio, such as propargylthio.

Lower alkoxy is, for example, C₁-C₇alkoxy, preferably C₁-C₄alkoxy, such as methoxy, ethoxy, propyloxy, isopropyloxy or butyloxy, but may also be isobutyloxy, secondary butyloxy, tertiary butyloxy or a pentyloxy, hexyloxy or heptyloxy group.

Lower alkyl is, for example, C₁-C₇alkyl, preferably C₁-C₄alkyl, such as especially methyl or, secondly, ethyl, propyl, isopropyl or butyl, but may also be isobutyl, secondary butyl, tertiary butyl or a C₅-C₇alkyl group, such as a pentyl, hexyl or heptyl group.

Lower alkylamino is, for example, C₁-C₇alkylamino, C₁-C₄alkylamino, such as especially methylamino, ethylamino, propylamino, isopropylamino or butylamino, but may also be isobutylamino, secondary butylamino, tertiary butylamino or a C₅-C₇alkylamino group, such as a pentylamino, hexylamino or heptylamino group.

Lower alkylcarbamoyl is, for example, C₁-C₇alkylcarbamoyl, preferably C₁-C₄alkylcarbamoyl, such as methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, but may also be isobutylcarbamoyl, secondary butylcarbamoyl, tertiary butylcarbamoyl or a C₅-C₇alkylcarbamoyl group, such as a pentylcarbamoyl, hexylcarbamoyl or heptylcarbamoyl group.

Lower alkylidene may be straight-chained or branched and is, for example, straight-chained or branched C₁-C₄alkylidene, such methylene, ethylidene, 1,1- or 2,2-propylidene or 1,1- or 2,2-butylidene.

Lower alkylene is, for example, straight-chained C₁-C₄alkylene, for example of the formula $-(CH_2)_n-$ (Ia) wherein n is, for example, 2, 3 or 4.

Lower alkynylene is, for example, straight-chained C₂-C₄alkynylene, for example of the formula $-C\equiv C-(CH_2)_{n-2}-$ (Ic) wherein n is, for example, 2, 3 or 4.

Lower alkenylene is, for example, straight-chained C₂-C₄alkenylene, for example of the formula $-CH=CH-(CH_2)_{n-2}-$ (Ib) wherein n is, for example, 2, 3 or 4.

Lower alkylphosphono is, for example, C₁-C₇alkylphosphono, such as methylphosphono, ethylphosphono, propylphosphono, isopropylphosphono or butylphosphono, but may also be isobutylphosphono, secondary butylphosphono, tertiary butylphosphono or a C₅-C₇alkylphosphono group, such as a pentylphosphono, hexylphosphono or heptylphosphono group.

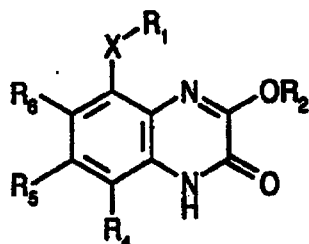
Lower alkylthio is, for example, C₁-C₇alkylthio, preferably C₁-C₄alkylthio, such as methylthio, ethylthio, propylthio or butylthio, but may also be a pentylthio, hexylthio or heptylthio group.

N-Phenyl-N-lower alkyl-carbamoyl is, for example, N-phenyl-C₁-C₄alkyl-carbamoyl, such as N-methyl-N-phenyl-carbamoyl, N-ethyl-N-phenyl-carbamoyl, N-phenyl-N-propyl-carbamoyl or N-butyl-N-phenyl-carbamoyl.

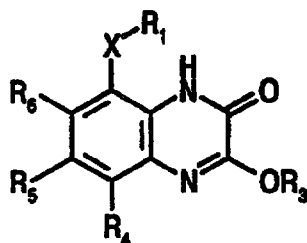
Phenyl-lower alkoxy-carbonyl is, for example, unsubstituted or C₁-C₄alkyl-, C₁-C₄alkoxy-, hydroxy-, halo- and/or trifluoromethyl-substituted phenyl-C₁-C₄alkoxy-carbonyl, such as benzyloxy-carbonyl or α -phenylethoxy-carbonyl.

Tautomers come into consideration especially in the case of compounds of formula I wherein one or both radicals R₁ and R₂ are hydrogen. Tautomers of such compounds of formula I are best described by the structural formula I', I'' or I'''

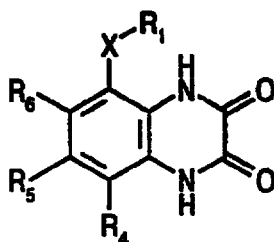
- 6 -



(I'),



(I'') or



(I''').

Compounds of formula I may form salts with bases or, when at least one of the radicals R₄, R₅ and R₆ is unsubstituted or aliphatically substituted amino, may form internal salts.

Salts of compounds of formula I with bases are, for example, salts thereof with pharmaceutically acceptable bases, such as non-toxic metal salts derived from metals of groups Ia, Ib, IIa and IIb, for example alkali metal salts, especially sodium or potassium salts, alkaline earth metal salts, especially calcium or magnesium salts, and also ammonium salts with ammonia or organic amines or quaternary ammonium bases, such as optionally C-hydroxylated aliphatic amines, especially mono-, di- or tri-lower alkylamines, for example methyl-, ethyl- or diethyl-amine, mono-, di- or tri-(hydroxy-lower alkyl)amines, such as ethanol-, diethanol- or triethanol-amine, tris(hydroxymethyl)methylamine or 2-hydroxy-tert-butylamine, or N-(hydroxy-lower alkyl)-N,N-di-lower alkylamines or N-(polyhydroxy-lower alkyl)-N-lower alkylamines, such as 2-(dimethylamino)ethanol or D-glucamine, or quaternary aliphatic ammonium hydroxides, for example tetrabutylammonium hydroxide.

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Also included are both total salts and, depending on the number of acid groups, partial salts, that is to say salts with 1, 2 or 3, preferably 2, equivalents of base per mole of acid of formula I, or salts with 1, 2 or 3 equivalents, preferably 1 equivalent, of acid per mole of base of formula I.

For the purposes of isolation or purification it is also possible to use pharmaceutically unacceptable salts. Only the pharmaceutically acceptable, non-toxic salts are used therapeutically and they are therefore preferred.

The compounds of formula I have valuable pharmacological properties. In particular, they have a pronounced and selective antagonistic action with respect to N-methyl-D-aspartic-acid-sensitive (NMDA-sensitive) excitatory amino acid receptors of warm-blooded animals. That can be demonstrated *in vitro*, for example, in the experimental procedure according to Sillis M., Fagg G., Pozza M., Angst Ch., Brundish D., Hurt S., Wilusz E., Williams M.: [³H]CGP 39653: a new N-methyl-D-aspartate antagonist radioligand with low nanomolar affinity in rat brain. Eur. J. Pharmacol. 192, pages 19-24 (1991). In that experimental procedure it is determined to what extent the binding of L-³H-glutamic acid to NMDA-sensitive receptors is inhibited. The concentration required for 50 % displacement (IC₅₀) lies in the nano- and lower milli-molar range, that is to say at concentrations of approximately from 0.0005 to 1 µmol. The NMDA-antagonistic properties of the novel compounds can, however, also be demonstrated *in vivo*, for example in the mouse, with reference to their inhibitory action against NMDA-induced convulsions.

By virtue of those properties, the compounds of formula I and the pharmaceutically acceptable salts thereof are excellently suitable for the treatment of pathological conditions that are responsive to blocking of NMDA-sensitive receptors, for example ischaemic disorders, such as cerebral ischaemia, and ischaemic disorders of the eyes, vascular and muscular spasms, such as migraine or local or general spasticity, and especially convulsions, such as epilepsy.

The anticonvulsive properties of the compounds according to the invention can be determined, for example, in the mouse with reference to their pronounced protective action with respect to convulsions induced by electric shock or audiogenically, it being possible to use, for example, the established electric shock mouse model or the experimental procedure

according to Chapman et al., *Arzneimittel-Forsch.* **34**, 1261 (1984). In the electric shock mouse model, for example the compounds according to the invention have an ED₅₀ of approximately from 1 to 10 mg/kg i.p..

The antispastic properties on which the suitability of the compounds provided according to the invention for the treatment of migraine is based can be demonstrated, for example, in the rat with reference to their depression-inhibiting action in accordance with the experimental procedure of R. Marannes *et al.*, *Brain Res.* **457**, 226 (1988). In that model, the compounds provided according to the invention lower the threshold of "spreading depression", and reduce its duration, in a dosage range of approximately from 3 to 30 mg/kg i.p..

The invention relates especially to compounds of formula I wherein

R₁ is lower alkylphosphono,

R₂ and R₃ are each independently of the other hydrogen, lower alkyl, lower alkenyl or lower alkynyl, such as propargyl,

the radicals R₄, R₅ and R₆ are each independently of the others hydrogen, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, mercapto, lower alkylthio, lower alkanesulfinyl, lower alkanesulfonyl, lower alkenylthio, lower alkynylthio, lower alkenesulfinyl, lower alkanesulfonyl, amino, lower alkylamino, di-lower alkylamino, nitro, carboxy, lower alkoxy-carbonyl; unsubstituted or lower alkyl-, lower alkoxy-, hydroxy-, halo- and/or trifluoromethyl-substituted phenyl-lower alkoxy-carbonyl; carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl; phenylcarbamoyl or N-phenyl-N-lower alkylcarbamoyl, each of which is unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; cyano, phosphono, lower alkylphosphono, di-lower alkylphosphono, halogen or trifluoromethyl, and X is lower alkylidene, lower alkylene, lower alkenylene or lower alkynylene, and to the tautomers and/or salts thereof.

The invention relates above all to compounds of formula I wherein

R₁ is phosphono,

R₂ and R₃ are each independently of the other hydrogen or C₁-C₄alkyl, such as methyl or ethyl,

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the radicals R_4 , R_5 and R_6 are each independently of the others hydrogen, C_1 - C_4 alkyl, such as methyl or ethyl, C_1 - C_4 alkoxy, such as methoxy or ethoxy, C_1 - C_4 alkylthio, such as methylthio, amino, nitro, carboxy, C_1 - C_4 alkoxycarbonyl, such as methoxy- or ethoxy-carbonyl, carbamoyl, C_1 - C_4 alkylcarbamoyl, such as methylcarbamoyl, di- C_1 - C_4 alkylcarbamoyl, such as dimethylcarbamoyl, halogen or trifluoromethyl, and

X is C_1 - C_4 alkylidene, such as methylene, ethylidene, 1,1- or 2,2-propylidene or 1,1- or 2,2-butylidene, C_1 - C_4 alkylene, for example of the formula $-(CH_2)_n-$ (Ia), C_2 - C_4 alkenylene, for example of the formula $-CH=CH-(CH_2)_{n-2}-$ (Ib), or C_2 - C_4 alkynylene, for example of the formula $-C\equiv C-(CH_2)_{n-2}-$ (Ic), n in each case being, for example, 2, 3 or 4,

and to the tautomers and/or salts thereof.

The invention relates especially to compounds of formula I wherein

R_1 is phosphono,

R_2 is hydrogen or C_1 - C_4 alkyl, such as methyl or ethyl,

R_3 is hydrogen,

the radicals R_4 , R_5 and R_6 are each independently of the others hydrogen, C_1 - C_4 alkyl, such as methyl or ethyl, nitro, halogen or trifluoromethyl, and

X is C_1 - C_4 alkylidene, such as methylene or ethylidene, or a group of the formula

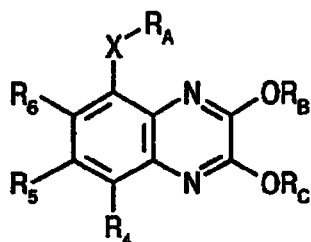
$-(CH_2)_n-$ (Ia), $-CH=CH-(CH_2)_{n-2}-$ (Ib) or $-C\equiv C-(CH_2)_{n-2}-$ (Ic), n in each case being 2, 3 or 4,

and to the tautomers and/or salts thereof.

The invention relates specifically to the compounds of formula I mentioned in the Examples and to the salts thereof, especially the pharmaceutically acceptable salts thereof.

The process for the preparation of the compounds according to the invention comprises removing the phosphono-protecting group, and, if desired, the group(s) R_B and/or R_C , from a compound of formula II

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(II),

wherein R_A is a protected phosphono group, R_B is a group R_2 or a hydroxy-protecting group, R_C is a group R_3 or a hydroxy-protecting group, and R_4 , R_5 and R_6 are as defined, and if desired converting the resulting compound into a different compound of formula I, separating a mixture of isomers obtainable according to the process into its components and isolating the particular preferred isomer and/or converting a free compound obtainable according to the process into a salt or converting a salt obtainable according to the process into the corresponding free compound.

Suitable as phosphono-protecting groups and hydroxy-protecting groups are customary phosphono- and hydroxy-protecting groups known in the prior art. Protected phosphono groups R_A are especially in ester form, for example in the form of esterified phosphono, such as di-lower alkylphosphono or unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or nitro-substituted diphenyl- or dibenzyl-phosphono groups. Suitable as protected hydroxy groups R_B and R_C are, in addition to groups R_1 and R_2 , especially silyl groups, such as tri-lower alkylsilyl, for example trimethylsilyl, also unsubstituted or lower alkyl-, lower alkoxy-, halo- and/or nitro-substituted phenyl or benzyl groups.

The mentioned protecting groups are removed in customary manner, for example by solvolysis or hydrogenolysis.

For example, treatment of a compound of formula II wherein R_A is esterified phosphono, R_B is a group R_2 other than hydrogen and R_C is a group R_3 other than hydrogen with an acid hydrolysing agent yields, for example, a compound of formula I wherein R_1 is phosphono and R_2 and R_3 are hydrogen. Acid hydrolysing agents are, for example, mineral acids, such as hydrohalic acid or sulfuric acid, if necessary in admixture with a protic solvent, such as acetic acid. Such agents are, for example, from approximately 30 % to approximately 35 % solutions of hydrobromic acid in acetic acid, mixtures of concentrated, for example approximately 35 %, hydrochloric acid in acetic acid or mixtures of equal parts of

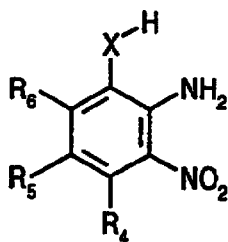
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concentrated, for example approximately 35 %, hydrochloric acid or concentrated sulfuric acid, water and acetic acid. The reaction is advantageously carried out at elevated temperature, for example in a temperature range of from approximately 80°C to approximately 120°C, for example at boiling temperature.

It is also possible, however, to control the reaction in customary manner so that esterified phosphono, such as di-lower alkylphosphono, is only partially solvolysed, for example to the lower alkylphosphono stage, and/or only one of the hydroxy-protecting groups R_B and R_C is removed. For example, treatment of a compound of formula II wherein R_A is esterified phosphono, R_B is a group R_2 other than hydrogen and R_C is a group R_3 other than hydrogen with a tri-lower alkylhalosilane or hexamethyl disilazane and then with a lower alkanol, lower alkenol or lower alkynol, yields a compound of formula I wherein R_1 is phosphono, R_3 is hydrogen and R_2 is lower alkyl, lower alkenyl or lower alkynyl. The reaction with the silyl compound is advantageously carried out in a halogenated hydrocarbon, such as dichloromethane, and the further reaction with the alcohol is advantageously carried out in the presence of water.

Starting materials of formula II wherein X is lower alkylidene can be prepared, for example, as follows:

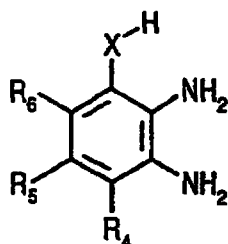
in a compound of formula III



(III),

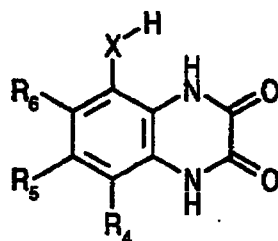
wherein R_4 , R_5 , R_6 and X are as defined, the nitro group is reduced to amino in customary manner, for example by hydrogenation in the presence of a hydrogenation catalyst, such as Raney nickel; the resulting compound of formula IV

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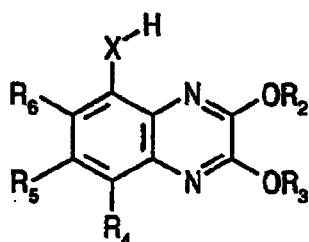
(IV)

is reacted in customary manner with oxalic acid or a reactive derivative thereof, such as an oxalic acid diester, for example with diethyl oxalate; in the resulting quinoxaline-2,3-dione of formula V



(V)

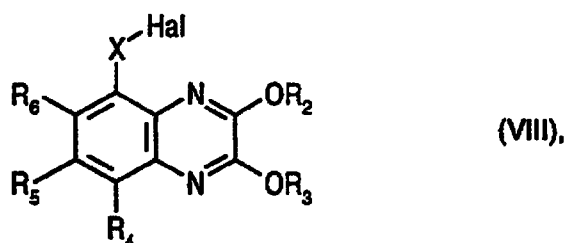
the oxo groups are converted in customary manner, for example by treatment with phosphorus oxychloride and/or phosphorus pentachloride and subsequent reaction with an alcohol of the formula $R_2\text{-OH}$ (VIa) or $R_3\text{-OH}$ (VIb), into groups of the formula -OR_2 or -OR_3 ; in the resulting compound of formula VII



(VII)

the group -X-H is halogenated in customary manner, for example using N-bromosuccinimide, in the α -position relative to the benzo ring and, in order to prepare a compound of formula II wherein R_4 is esterified phosphono, such as di-lower alkylphosphono, the resulting compound of formula VIII

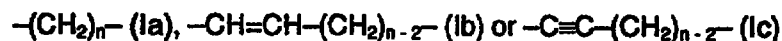
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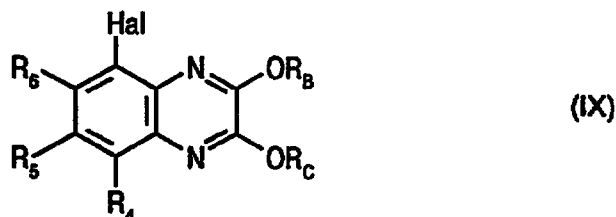
wherein Hal is halogen, for example bromine, is reacted with a phosphonous acid triester, such as a tri-lower alkyl phosphite, such as trimethyl or triethyl phosphite.

In that method of synthesising compounds of formula II, the introduction of substituents R_4 , R_5 and/or R_6 that are other than hydrogen is effected preferably at the stage of the intermediates of formula III.

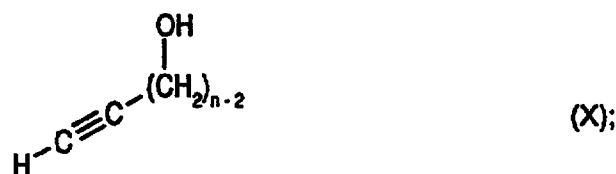
Compounds of formula II wherein X is a divalent aliphatic radical X' other than lower alkylidene and is, for example, a group of the formula



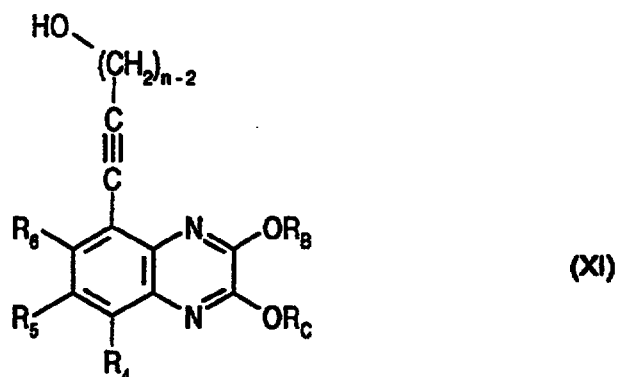
wherein n is 2, 3 or 4 can be prepared, for example, by reacting a compound of formula IX



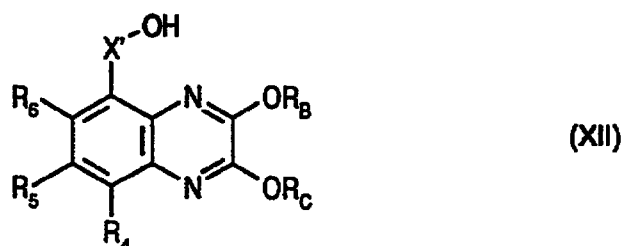
In customary manner, for example in the presence of palladium/triphenylphosphine, advantageously in dimethylformamide at from approximately 80 to approximately 120°C, with a compound of formula X



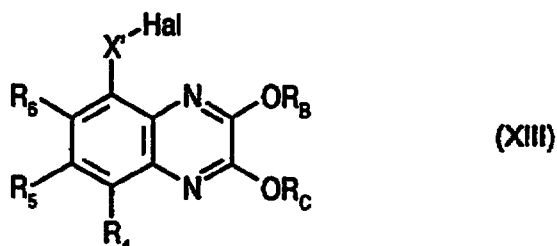
if desired, in the resulting compound of formula XI



reducing the extracyclic triple bond to a double or single bond in customary manner, for example by catalytic hydrogenation, preferably in the presence of palladium on carbon; halogenating a resulting compound of formula XII

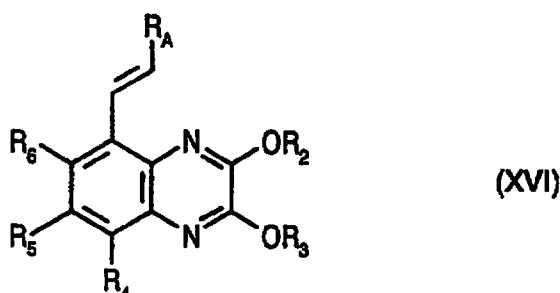


in customary manner, for example by reaction with an agent that introduces halogen Hal, for example by reaction with 1,1'-carbonyldiimidazole and subsequent quaternisation of the imidazolo group, for example by means of a lower alkyl halide, and reacting the resulting halogen compound of formula XIII



further in customary manner, for example as described above, with an agent that introduces the group R_A , such as a phosphonous acid triester, for example a tri-lower alkyl phosphite, such as trimethyl or triethyl phosphite. That process is especially suitable for the preparation of compounds of formula II wherein R_A is an esterified phosphono group, such as di-lower alkylphosphono, and n is 3 or 4.

For the preparation of compounds of formula II wherein X is a group of the formula $-\text{CH}=\text{CH}-$ (Ic1) or Ia, for example a compound of formula VIII or XIII is used as starting material, the terminal halomethyl group is converted into formyl in customary manner, for example by reaction with 2-nitropropane in alcoholic solution, the resulting aldehyde is reacted in customary manner with a methanediphosphonic acid tetra-lower alkyl ester to form the corresponding compound of formula XVI



and, if desired, the extracyclic double bond is hydrogenated to the single bond. Resulting intermediates wherein X has at least one hydrogen atom in the α -position relative to the benzo ring, i.e. is 1,1-lower alkylidene, for example methylene, are converted in customary manner, for example by treatment with an alkali metal disilazide, for example sodium tetramethyl disilazide, and then with an alkylating agent, such as a lower alkyl iodide of the formula R-I, into the corresponding compounds of the formula wherein X is a lower alkylidene radical, for example of the formula $>\text{X}-\text{R}$ or $-\text{X}(\text{R})-\text{R}$, that is bonded *via* a chain member.

Compounds obtainable in accordance with the process can be converted in customary manner into other compounds of formula I.

For example, a compound of formula I wherein R_1 is partially esterified phosphono can be hydrolysed in customary manner to form the corresponding compound of the formula wherein R_1 is phosphono.

In addition, a compound of formula I wherein R_2 and/or R_3 is an aliphatic radical can be solvolysed in customary manner to form the corresponding compound of formula I wherein R_2 and/or R_3 is hydrogen, or the corresponding tautomer of formula I', for example as described above for the removal of hydroxy-protecting groups R_B and R_C . Conversely, a

compound of formula I wherein R_2 and/or R_3 is hydrogen, or a tautomer thereof of formula I', I'' and/or I''', can be converted by the introduction of an aliphatic radical in customary manner, for example by treatment with a strong halogenating agent, such as phosphorus oxychloride and/or phosphorus pentachloride, and then with an aliphatic alcohol, into the corresponding compound of formula I wherein R_2 and/or R_3 is an aliphatic radical, or into the corresponding tautomer of formula I', I'' or I'''.

In addition, a resulting compound of formula I wherein at least one of the radicals R_4 , R_5 and R_6 is etherified mercapto, for example lower alkylthio, can be oxidised in customary manner to the corresponding compound of formula I wherein R_4 , R_5 and/or R_6 is oxidised esterified mercapto, for example lower alkanesulfinyl or lower alkanesulfonyl.

In addition, in compounds of formula I wherein at least one of the radicals R_4 , R_5 and R_6 is hydrogen, the hydrogen atom can be replaced by a radical R_4 , R_5 or R_6 that is other than hydrogen. For example, halogenation, nitration or the introduction of lower alkanoyl can be carried out in customary manner, the latter, for example, by reaction with a reactive lower alkanoyl acid derivative, such as a lower alkanoyl acid chloride, in the presence of aluminium trichloride, preferably in a halogenated hydrocarbon, if necessary at boiling temperature. In addition, nitro can be converted into amino in customary manner, for example by reduction, and halogen can be removed in customary manner, for example by hydrogenolysis.

Resulting salts can be converted into the free compounds in a manner known *per se*, for example by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or metal hydrogen carbonate, or another salt-forming base mentioned at the beginning, or with an acid, such as a mineral acid, for example with hydrochloric acid, or another salt-forming acid mentioned at the beginning.

Resulting salts can be converted into different salts in a manner known *per se*; acid addition salts, for example, by treatment with a suitable metal salt, such as a sodium, barium or silver salt, of a different acid in a suitable solvent in which an inorganic salt being formed is insoluble and is therefore eliminated from the reaction equilibrium, and basic salts by freeing of the free acid and conversion into a salt again.

The compounds of formula I, including their salts, may also be obtained in the form of hydrates or may include the solvent used for crystallisation.

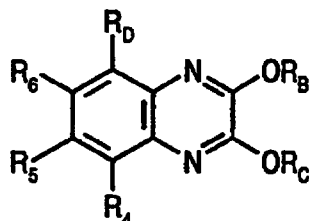
In view of the close relationship between the novel compounds in free form and in the form of their salts, hereinabove and hereinbelow any reference to the free compounds and their salts is to be understood as including also the corresponding salts and free compounds, respectively, as appropriate and expedient.

Resulting diastereoisomeric mixtures and mixtures of racemates can be separated into the pure diastereoisomers or racemates in known manner on the basis of the physico-chemical differences between the constituents, for example by chromatography and/or fractional crystallisation.

Resulting racemates can also be resolved into the optical antipodes in accordance with known methods, for example by recrystallisation from an optically active solvent, with the aid of microorganisms or by reaction of the resulting diastereoisomeric mixture or racemate with an optically active auxiliary compound, for example depending on the acidic, basic or functionally modifiable groups present in compounds of formula I, with an optically active acid, base or an optically active alcohol, to form mixtures of diastereoisomeric salts or functional derivatives, such as esters, and separation thereof into the diastereoisomers from which the desired enantiomer can be freed in the appropriate customary manner. Bases, acids and alcohols suitable for that purpose are, for example, optically active alkaloid bases, such as strychnine, cinchonine or brucine, or D- or L-(1-phenyl)ethylamine, 3-pipecoline, ephedrine, amphetamine and similar synthetically obtainable bases, optically active carboxylic or sulfonic acids, such as quinic acid or D- or L-tartaric acid, D- or L-di-o-toluyltartaric acid, D- or L-malic acid, D- or L-mandelic acid or D- or L-camphorsulfonic acid, and optically active alcohols, such as borneol or D- or L-(1-phenyl)ethanol.

The invention relates also to those forms of the process according to which a compound obtainable as intermediate at any stage of the process is used as starting material and the remaining steps are carried out or a starting material is used in the form of a salt or, especially, is formed under the reaction conditions.

The invention relates also to the novel starting materials which have been developed specifically for the preparation of the compounds according to the invention, for example compounds of formula XVII



(XVII),

wherein

the radicals R_4 , R_5 and R_6 are each independently of the others hydrogen, an aliphatic hydrocarbon radical, free or etherified hydroxy, free or etherified mercapto or oxidised free or etherified mercapto, unsubstituted or aliphatically substituted amino, nitro, free or esterified or amidated carboxy, cyano, free or amidated sulfamoyl, halogen or trifluoromethyl,

R_B is a group R_2 or a hydroxy-protecting group, such as lower alkoxy or phenyl-lower alkoxy,

R_C is a group R_3 or a hydroxy-protecting group, such as lower alkoxy or phenyl-lower alkoxy, and

R_D is a group of the formula

$-(CH_2)_n-R_E$ (XVIIa), $-(CH_2)_{n-1}-CH=O$ (XVIIb), $-C\equiv C-(CH_2)_{n-2}-R_E$ (XVIIc),

$-C\equiv C-(CH_2)_{n-2}-CH=O$ (XVIIId), $-CH=CH-(CH_2)_{n-2}-R_E$ (XVIIe) or

$-CH=CH-(CH_2)_{n-2}-CH=O$ (XVIIIf),

wherein R_E is free or reactive esterified hydroxy, such as hydroxy, halogen, lower alkane-sulfonyloxy, or unsubstituted or lower alkyl-, halo- and/or nitro-substituted benzenesulfonyloxy or naphthalenesulfonyloxy,

and n is 2, 3 or 4,

especially to the group of starting materials leading to the compounds of formula I described at the beginning as being preferred, to the processes for the preparation thereof and to the use thereof as intermediates.

The invention relates also to pharmaceutical compositions comprising the compounds according to the invention or pharmaceutically acceptable salts thereof as active ingredients, and to processes for the preparation thereof.

The pharmaceutical compositions according to the invention, which comprise the compounds according to the invention or pharmaceutically acceptable salts thereof, are for enteral, such as oral and also rectal, and parenteral administration to (a) warm-blooded animal(s), the compositions comprising the pharmacological active ingredient alone or together with a pharmaceutically acceptable carrier. The daily dose of the active ingredient depends upon age and individual condition and upon the mode of administration.

The novel pharmaceutical compositions comprise, for example, from approximately 10 % to approximately 80 %, preferably from approximately 20 % to approximately 60 %, active ingredient. Pharmaceutical compositions according to the invention for enteral or parenteral administration are, for example, those in unit dose forms, such as dragées, tablets, capsules or suppositories, and also ampoules. They are prepared in a manner known *per se*, for example by means of conventional mixing, granulating, confectioning, dissolving or lyophilising processes. For example, pharmaceutical compositions for oral administration can be obtained by combining the active ingredient with solid carriers, optionally granulating a resulting mixture, and processing the mixture or granules, if desired or necessary, after the addition of suitable excipients, to form tablets or dragée cores.

Suitable carriers are especially fillers, such as sugars, for example lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, for example tri-calcium phosphate or calcium hydrogen phosphate, and also binders, such as starch pastes using, for example, corn, wheat, rice or potato starch, gelatin, tragacanth, methylcellulose and/or polyvinylpyrrolidone, if desired disintegrators, such as the above-mentioned starches, and also carboxymethyl starch, cross-linked polyvinylpyrrolidone, agar, alginic acid or a salt thereof, such as sodium alginate. Excipients are especially flow agents, flow-conditioners and lubricants, for example silicic acid, talc, stearic acid or salts thereof, such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with suitable, optionally enteric, coatings, there being used *inter alia* concentrated sugar solutions which may contain gum arabic, talc, polyvinylpyrrolidone, polyethylene glycol and/or titanium dioxide, or coating solutions in suitable organic solvents or solvent mixtures

or, for the preparation of enteric coatings, solutions of suitable cellulose preparations, such as acetylcellulose phthalate or hydroxypropylmethylcellulose phthalate. Dyes or pigments may be added to the tablets or dragée coatings, for example for identification purposes or to indicate different doses of active ingredient.

Other orally administrable pharmaceutical compositions are hard gelatin capsules and also soft, sealed capsules consisting of gelatin and a plasticiser, such as glycerol or sorbitol. The hard gelatin capsules may comprise the active ingredient in the form of granules, for example in admixture with fillers, such as lactose, binders, such as starches, and/or glidants, such as talc or magnesium stearate, and if desired stabilisers. In soft capsules the active ingredient is preferably dissolved or suspended in suitable liquids, such as fatty oils, paraffin oil or liquid polyethylene glycols, it likewise being possible to add stabilisers.

Suitable rectally administrable pharmaceutical compositions are, for example, suppositories that consist of a combination of the active ingredient with a suppository base material. Suitable suppository base materials are, for example, natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. It is also possible to use gelatin rectal capsules which comprise a combination of the active ingredient with a base material. Suitable base materials are, for example, liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

For parenteral administration there are suitable, especially, aqueous solutions of an active ingredient in water-soluble form, for example in the form of a water-soluble salt, and also suspensions of the active ingredient, such as corresponding oily injection suspensions, there being used suitable lipophilic solvents or vehicles, such as fatty oils, for example sesame oil, or synthetic fatty acid esters, for example ethyl oleate or triglycerides, or aqueous injection suspensions which comprise viscosity-increasing substances, for example sodium carboxymethylcellulose, sorbitol and/or dextran, and optionally also stabilisers.

The dose of the active ingredient depends upon the species of warm-blooded animal, age and individual condition and also upon the mode of administration. In a normal case the approximate daily dose for oral administration to a patient weighing about 75 kg is estimated to be from approximately 10 mg to approximately 500 mg.

The following Examples serve to illustrate the invention; temperatures are given in degrees Celsius, pressures in mbar.

Example 1: 7-Bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid
0.68 g (1.62 mmol) of 7-bromo-2,3-dimethoxy-quinoxalin-5-ylmethanephosphonic acid diethyl ester are heated for 15 minutes at 130° in 20 ml of a 33 % solution of hydrobromic acid in acetic acid. The reaction mixture is allowed to cool to room temperature, 80 ml of diethyl ether are added and stirring is carried out for 30 minutes. The crystalline precipitate is filtered off, washed with diethyl ether and dried, yielding the title compound; m.p. > 300°; ¹H-NMR (300 MHz) in DMSO-d₆; δ (ppm) = 12.02 (s, 1H); 11.30-11.70 (m, 1H); 7.18 (m, 2H); 3.32 (d, 2H, J=22.5 Hz).

The starting material can be prepared, for example, as follows:

a) 7-Bromo-5-methyl-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline
22.6 ml (440 mmol) of bromine are added dropwise to a solution of 55.7 g (366 mmol) of 2-methyl-6-nitro-aniline in 500 ml of acetic acid. A suspension is formed. The suspension is stirred for 1 hour at room temperature, poured into 2000 ml of ice-water and filtered with suction. Washing with water and drying yield an orange-coloured solid. 40 g thereof are dissolved in 600 ml of ethanol, 6 g of Raney nickel are added and shaking is carried out under a hydrogen atmosphere until 12 300 ml of hydrogen have been taken up. The catalyst is filtered off through diatomaceous earth and the filter cake is washed thoroughly with ethanol. The filtrate and the washing solutions are combined and concentrated by evaporation under reduced pressure. The evaporation residue is taken up in 1000 ml of 2N hydrochloric acid, 31.15 g (346 mmol) of oxalic acid are added and heating under reflux is carried out overnight. The reaction mixture is then allowed to cool to room temperature, poured into 1000 ml of ice-water, filtered with suction, washed with water and dried. The resulting solid is made into a slurry in a small amount of acetone, stirred for 30 minutes, filtered with suction again, washed first with acetone and then with diethyl ether and dried, yielding the title compound in the form of a brownish solid, m.p. > 300°; ¹H-NMR (200 MHz) in DMSO-d₆; δ (ppm) = 11.95 (s, 1H); 11.31 (s, 1H); 7.13 (s, 2H); 2.32 (s, 3H).

b) 7-Bromo-2,3-dimethoxy-quinoxalin-5-ylmethanephosphonic acid diethyl ester

38.13 g (149.5 mmol) of 7-bromo-5-methyl-2,3-dioxo-1,2,3,4-tetrahydro-quinoxaline and 68.5 g (329 mmol) of phosphorus pentachloride are carefully mixed, finely ground and, in a sulfonating flask, heated slowly to 160°, whereupon phosphorus oxychloride begins to distil off. The reaction mixture is slowly heated further to 200° until no further phosphorus oxychloride is separated off, then allowed to cool and poured into 2000 ml of water. The precipitate that has separated out is filtered off with suction, washed with water and dried and then taken up in 2000 ml of dichloromethane and filtered. The filter residue is washed with dichloromethane and the combined filtrates are dried over magnesium sulfate, concentrated by evaporation and dried, yielding 25 g of 7-bromo-2,3-dichloro-5-methyl-quinoxaline in the form of a brownish solid which is made into a slurry in 300 ml of methanol. A solution of 227 mmol of sodium methanolate in 47 ml of methanol is added thereto. Heating is carried out at reflux for 3 hours, the excess methanol is removed and the remaining product is partitioned between 500 ml of ethyl acetate and 500 ml of water. The aqueous phase is extracted by shaking again with 500 ml of ethyl acetate. The organic phases are washed in succession with 300 ml of water and 300 ml of saturated sodium chloride solution, combined and dried over magnesium sulfate. Concentration by evaporation and crystallisation from methanol yield 16.39 g of 7-bromo-2,3-dimethoxy-5-methyl-quinoxaline in the form of white crystals. 14.72 g of those crystals, 10.6 g (59.6 mmol) of N-bromosuccinimide and 0.86 g (5.2 mmol) of AIBN are heated at reflux in 300 ml of tetrachloromethane for 4 hours. After filtration, the filter residue is washed with tetrachloromethane and the combined filtrates are concentrated by evaporation. Under nitrogen, the evaporation residue (7-bromo-2,3-dimethoxy-5-bromomethyl-quinoxaline) is heated at reflux in triethyl phosphite for 15 hours. The excess triethyl phosphite is removed and the residue is purified by chromatography on silica gel with ethyl acetate as eluant, yielding the title compound; ¹H-NMR (200 MHz) in DMSO-d₆; δ (ppm) = 7.8 (m, 1H); 7.65 (s, 1H); 4.03 (s, 3H); 3.96 (m, 4H); 3.75 (d, 2H, J=22.5 Hz); 1.10 (t, 6H, J=7 Hz).

Example 2: 2,3-Dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid

4.21 g (10.8 mmol) of 7-bromo-2,3-dimethoxy-quinoxalin-5-ylmethanephosphonic acid dimethyl ester and 1.2 g of triethylamine are dissolved in 100 ml of methanol, 0.4 g of palladium on carbon is added and the reaction mixture is stirred under a hydrogen atmosphere until 258 ml of hydrogen have been taken up. The catalyst is filtered off, and washing with methanol and concentration to dryness by evaporation are carried out. The

residue is dissolved in 20 ml of acetic acid; 20 ml of water and 20 ml of concentrated hydrochloric acid are added and heating at reflux is carried out for 24 hours. The reaction mixture is allowed to cool to room temperature, poured into 200 ml of water, filtered with suction, washed with water, acetone and diethyl ether and allowed to dry, yielding the title compound in the form of dirty-white crystals; m.p. $>280^{\circ}$; $^1\text{H-NMR}$ (200 MHz) in DMSO-d_6 ; δ (ppm) = 12.0 (s, 1H); 11.6-11.1 (m, 1H); 7.03 (m, 3H); 3.30 (d, 2H, $J=20$ Hz).

The starting material can be prepared, for example, as follows:

a) 7-Bromo-2,3-dimethoxy-quinoxalin-5-ylmethanephosphonic acid dimethyl ester

16.39 g (57.9 mmol) of 7-bromo-2,3-dimethoxy-5-methyl-quinoxaline, 11.2 g (60.8 mmol) of N-bromosuccinimide and 0.514 g (3.13 mmol) of AIBN are heated at reflux in 300 ml of tetrachloromethane for 4 hours. After filtration, the filter residue is washed with dichloromethane. The combined filtrates are extracted by shaking in succession with 500 ml of 1N hydrochloric acid and saturated sodium chloride solution. The aqueous phases are extracted by shaking with dichloromethane and all the organic phases are combined, dried over magnesium sulfate and concentrated by evaporation. 21.0 g of a solid are obtained. 15.7 g thereof are dissolved in 200 ml of trimethyl phosphite and heated at reflux overnight. Then the excess trimethyl phosphite is removed and the residue is purified by chromatography on silica gel with ethyl acetate as eluant, yielding the title compound; $^1\text{H-NMR}$ (300 MHz) in DMSO-d_6 ; δ (ppm) = 7.83 (m, 1H); 7.66 (s, 1H); 4.08 (s, 3H); 4.05 (m, 3H); 3.87-3.58 (m, 8H).

Example 3: 7-Bromo-6-nitro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid

5.43 g (13.9 mmol) of 7-bromo-2,3-dimethoxy-quinoxalin-5-ylmethanephosphonic acid dimethyl ester and 1.45 g (18.0 mmol) of ammonium nitrate are heated at 60° in 10 ml of a mixture of equal parts of dichloromethane and trichloromethane. Then in the course of 1 hour 15.15 g (72.2 g) of acetic anhydride are added dropwise. The reaction mixture is stirred for 3 hours, allowed to cool to room temperature and extracted by shaking with 200 ml of water and twice with 200 ml of saturated sodium hydrogen carbonate solution each time. The aqueous phases are back-extracted with 200 ml of dichloromethane each. The combined organic phases are dried over magnesium sulfate and concentrated by evapora-

tion. The residue is purified by chromatography on silica gel first with ethyl acetate and then with ethyl acetate/diethyl ether (10:1) as eluant and crystallised from methanol. The resulting 7-bromo-6-nitro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid dimethyl ester is dissolved in 5 ml of acetic acid, 5 ml of water and 5 ml of concentrated hydrochloric acid and heated at reflux for 24 hours. The reaction mixture is allowed to cool to room temperature, concentrated to dryness by evaporation and crystallised from ethanol/diethyl ether, yielding the title compound in crystalline form; m.p. >250°; ¹H-NMR (300 MHz) in DMSO-d₆; δ (ppm) = 12.28 (s, 1H); 11.70 (s, 1H); 7.36 (d, 1H, J=3.75 Hz); 3.34 (d, 2H, J= 22.5 Hz).

Example 4: 1-(7-Bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid

5.23 ml of a 1 molar solution of sodium hexamethyl disilazide in tetrahydrofuran are added dropwise at -20° to a solution of 1.86 g (4.76 mmol) of 7-bromo-2,3-dimethoxy-quinoxalin-5-ylmethanephosphonic acid dimethyl ester in 20 ml of tetrahydrofuran. After 20 minutes, 6.75 g (47.6 mmol) of methyl iodide are added and the reaction mixture is heated at reflux for 3 hours, digested with 100 ml of saturated ammonium chloride solution and extracted by shaking twice with 200 ml of ethyl acetate each time. The extracts are combined, dried over magnesium sulfate, concentrated to dryness by evaporation and purified by chromatography on silica gel first with ethyl acetate and then with ethyl acetate/diethyl ether (10:1) as eluant. Crystallisation from methanol/diethyl ether yields the title compound; m.p. > 300°; ¹H-NMR (200 MHz) in DMSO-d₆; δ (ppm) = 12.02 (s, 1H); 11.90-11.60 (s, 1H); 7.30 (m, 1H); 7.19 (m, 1H); 3.68 (qd, 1H, J¹= 7.5 Hz, J²=22.5 Hz); 1.39 (dd, 3H, J¹= 7.5 Hz, J²= 17.5 Hz).

Example 5: 7-Bromo-3-methoxy-2-oxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid

7.47 g (48.8 mmol) of trimethylbromosilane are added dropwise at 0° to a solution of 1.91 g (4.88 mmol) of 7-bromo-2,3-dimethoxy-quinoxalin-5-ylmethanephosphonic acid dimethyl ester in 25 ml of dichloromethane. The reaction mixture is allowed to warm to room temperature and stirred overnight. The dichloromethane and the excess trimethylbromosilane are removed and the residue is dried for 3 hours at room temperature under 0.1 torr. The residue is dissolved in 20 ml of methanol, 0.3 ml of water is added and stirring is carried out for 3 hours. The precipitate that has separated out is filtered off with suction,

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washed with methanol and diethyl ether and dried, yielding the title compound; m.p. 245-250°; ¹H-NMR (200 MHz) in DMSO-d₆; δ (ppm) = 12.40 (s, 1H); 7.38 (m, 1H); 7.26 (m, 1H); 3.99 (s, 3H); 3.42 (d, 2H, J= 22.5 Hz).

Example 6: 7-Bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylacetic acid

Tetrabutylammonium cyanide is added to 2.35 g (6.5 mmol) of 7-bromo-2,3-dimethoxy-5-bromomethyl-quinoxaline in 40 ml of water and 40 ml of dichloromethane and the reaction mixture is stirred overnight. The organic phase is separated off and washed with water. The aqueous phase is back-extracted with dichloromethane. The organic phases are combined, dried over magnesium sulfate and concentrated by evaporation. The evaporation residue is purified by chromatography on silica gel with hexane/ethyl acetate (first 20:1, then 15:1, finally 10:1) and taken up in 10 ml of tetrahydrofuran. 5 ml of 2N hydrochloric acid are added and heating at reflux is carried out overnight. The reaction mixture is allowed to cool to room temperature, poured into 50 ml of water, filtered with suction, washed with water and dried. The filtration residue is made into a slurry in 3 ml of water; 3 ml of acetic acid and 3 ml of concentrated sulfuric acid are added and heating at reflux is carried out for 5 hours. The reaction mixture is allowed to cool to room temperature, poured into 50 ml of ice-water, filtered, washed with water and dried, yielding the title compound; m.p. > 280°; ¹H-NMR (200 MHz) in DMSO-d₆; δ (ppm) = 12.05 (s, 1H); 11.57 (s, 1H); 7.22 (m, 2H); 3.86 (s, 2H).

Example 7: 3-(7-Chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)propanephosphonic acid

0.584 g (1.45 mmol) of 3-(7-chloro-2,3-dimethoxy-quinoxalin-5-yl)propanephosphonic acid diethyl ester are heated at 110° for 20 minutes in 25 ml of a 33 % solution of hydrobromic acid in acetic acid. The reaction mixture is allowed to cool to room temperature, 80 ml of diethyl ether are added and stirring is carried out for 30 minutes. The crystalline precipitate is filtered off, washed with diethyl ether and dried, yielding the title compound; m.p. 220-222°.

The starting material can be prepared, for example, as follows:

a) 5-Iodo-2,3,7-trichloro-quinoxaline

406.9 g (1.953 mol) of phosphorus pentachloride are added to a mixture of 195.9 g (0.93 mol) of 7-chloro-5-iodo-quinoxaline-dione in 1200 ml of phosphorus oxychloride and

the reaction mixture is stirred under reflux for 18 hours. The excess phosphorus oxychloride is distilled off from the reaction mixture at a bath temperature of 150°C. The residue is poured into 6000 ml of ice-water, the resulting suspension is stirred for 2 hours, filtered with suction and washed with a large amount of water. The filtration residue is dried *in vacuo* at 60°C, yielding 5-iodo-2,3,7-trichloro-quinoxaline in the form of light-brown, crude crystals which can be reacted further without further purification.

b) 7-Chloro-2,3-dimethoxy-5-iodo-quinoxaline

205 g (0.828 mol) of 5-iodo-2,3,7-trichloro-quinoxaline are introduced into 2255 ml of methanol at room temperature and 463.9 ml of an approx. 5.4 molar solution of sodium methanolate in methanol are added. The reaction mixture is then heated at reflux and stirred for 18 hours. The reaction mixture is cooled to 0°C and the suspension is filtered with suction. The filtration residue is washed with methanol and dried *in vacuo* at 60°C and the crude product is purified by continuous extraction with diethyl ether, yielding 7-chloro-2,3-dimethoxy-5-iodo-quinoxaline having a melting point of 94-96°C.

c) 3-(7-Chloro-2,3-dimethoxy-quinoxalin-5-yl)-prop-2-yn-1-ol

12.9 g (36.8 mmol) of 7-chloro-2,3-dimethoxy-5-iodo-quinoxaline, 7.6 ml (128.4 mmol) of propargyl alcohol, 2.1 g (3 mmol) of bis(triphenylphosphine)palladium dichloride, 6.6 ml (47.4 mmol) of triethylamine and 0.34 g (1.8 mmol) of copper(I) iodide are introduced into 125 ml of dimethylformamide and heated at a bath temperature of 70°C. The reaction mixture is stirred at that temperature for 3.5 hours and then allowed to cool to room temperature. Ethyl acetate is added and the reaction mixture is extracted with water, 1N hydrochloric acid and brine. The aqueous phases are washed with ethyl acetate. The organic phases are combined, dried with sodium sulfate, filtered with suction and concentrated. Chromatography of the crude product on silica gel with hexane/ethyl acetate (3:1) yields 3-(7-chloro-2,3-dimethoxy-quinoxalin-5-yl)-prop-2-yn-1-ol in the form of brown crystals having a melting point of 137-140°C.

d) 3-(7-Chloro-2,3-dimethoxy-quinoxalin-5-yl)-propan-1-ol

2.05 g (7.36 mmol) of 3-(7-chloro-2,3-dimethoxy-quinoxalin-5-yl)-prop-2-yn-1-ol are hydrogenated in 20 ml of tetrahydrofuran with approx. 0.4 g of Raney nickel under normal pressure until twice the molar amount of hydrogen has been taken up. The hydrogenation mixture is filtered with suction over glass-fibre filters and the filtrate is concentrated, yielding

3-(7-chloro-2,3-dimethoxy-quinoxalin-5-yl)-propan-1-ol in the form of beige crystals having a melting point of 104-105°C.

e) 5-(3-Bromopropyl)-7-chloro-2,3-dimethoxy-quinoxaline

0.5 g (1.77 mmol) of 3-(7-chloro-2,3-dimethoxy-quinoxalin-5-yl)-propan-1-ol and 0.287 g (1.77 mmol) of 1,1'-carbonyldiimidazole are introduced into 5 ml of acetonitrile under N₂. 0.75 ml of allyl bromide is added and the reaction mixture is stirred at room temperature for 30 minutes and under reflux for 2 hours. The reaction mixture is cooled to room temperature, diethyl ether is added and extraction is carried out with water, 0.1N hydrochloric acid, saturated sodium hydrogen carbonate solution and brine. The aqueous phases are washed with diethyl ether. The organic phases are combined, dried with sodium sulfate, filtered over a layer of silica gel and concentrated, yielding 5-(3-bromopropyl)-7-chloro-2,3-dimethoxy-quinoxaline in the form of a yellow oil which is used further without further purification.

f) 3-(7-Bromo-2,3-dimethoxy-quinoxalin-5-yl)propanephosphonic acid diethyl ester

0.52 g (1.5 mmol) of 5-(3-bromopropyl)-7-chloro-2,3-dimethoxy-quinoxaline are dissolved in 10 ml of trimethyl phosphite and heated at reflux overnight. The excess trimethyl phosphite is then removed and the residue is purified by chromatography on silica gel with ethyl acetate as eluant, yielding the title compound.

Example 8: 3-(7-Chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-ynephosphonic acid

The title compound is obtained in a manner analogous to that described in Example 7, but with the modification that in Step e) 3-(7-chloro-2,3-dimethoxy-quinoxalin-5-yl)-prop-2-yn-1-ol is used instead of 3-(7-chloro-2,3-dimethoxy-quinoxalin-5-yl)-propan-1-ol.

Example 9: 3-(7-Chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-enephosphonic acid

The title compound is obtained in a manner analogous to that described in Example 7, but with the modification that in Step d) hydrogenation is carried out until an equimolar amount of hydrogen has been taken up.

Example 10: 2-(7-Bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethenephosphonic acid

0.88 g (1.5 mmol) of 2-(7-bromo-2,3-dimethoxy-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethenediphosphonic acid tetraethyl ester are heated at 110° for 30 minutes in 30 ml of a 33 % solution of hydrobromic acid in acetic acid. The reaction mixture is allowed to cool to room temperature, 100 ml of diethyl ether are added, stirring is carried out for 30 minutes and the crystalline precipitate is filtered off, washed with diethyl ether and dried, yielding the title compound; m.p. >300°.

The starting material can be prepared, for example, as follows:

a) 7-Bromo-5-formyl-2,3-dimethoxy-quinoxaline

At 0°C, under N₂, 1.38 g (60 mmol) of sodium are dissolved in portions in 200 ml of methanol. At 0°C, 5.85 ml (65 mmol) of 2-nitropropane are added dropwise. Then 18.1 g (50 mmol) of 5-(bromomethyl)-7-bromo-2,3-dimethoxy-quinoxaline are added. The beige suspension is heated at reflux and stirred for 1 hour. The reaction mixture is poured into 600 ml of water and the methanol is distilled off. The residue is extracted twice with ethyl acetate and the organic phases are dried with sodium sulfate and filtered with suction. The filtrate is concentrated and the residue is dried under a high vacuum, yielding 7-bromo-5-formyl-2,3-dimethoxy-quinoxaline in the form of beige crystals having a melting point of 179-182°C.

b) 2-(7-Bromo-2,3-dimethoxy-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethenediphosphonic acid tetraethyl ester

At 0°C, under N₂, 0.35 g (15.5 mmol) of sodium is dissolved in portions in 50 ml of ethanol. At 0°C, with stirring, 2.9 g (10 mmol) of methanediphosphonic acid tetraethyl ester are added dropwise thereto, the reaction mixture is allowed to warm to room temperature and 2.97 g (10 mmol) of 7-bromo-5-formyl-2,3-dimethoxy-quinoxaline are added. The reaction mixture is stirred for 2 hours, poured into 200 ml of ice-water, neutralised with hydrochloric acid and extracted by shaking three times with 50 ml of diethyl ether each time. The combined ether extracts are dried over sodium sulfate and concentrated by evaporation under reduced pressure, yielding the title compound in the form of a yellowish oil that can be reacted further without further purification.

Example 11: 2-(7-Bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid

In a manner analogous to that described in Example 10, but with the modification that the intermediate according to Step b) is hydrogenated in the presence of 0.5 g of Raney nickel until an equimolar amount of hydrogen has been taken up.

Example 12: 4-(7-Chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)butanephosphonic acid

The title compound is obtained in a manner analogous to that described in Example 7, but with the modification that, in Step c), instead of propargyl alcohol the corresponding amount of but-3-ynol is added.

Example 13: In a manner analogous to that described in Examples 1 to 12, the following compounds can also be prepared:

- 1-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid;
- 2-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid;
- 3-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)propanephosphonic acid;
- 4-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)butanephosphonic acid;
- 4-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-1-enephosphonic acid;
- 4-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-3-enephosphonic acid;
- 2-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethenephosphonic acid;
- 3-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-enephosphonic acid;
- 3-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-ynephosphonic acid;
- 4-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-3-enephosphonic acid;
- 3-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)propanephosphonic acid;
- 4-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)butanephosphonic acid;
- 3-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-enephosphonic acid;
- 3-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-ynephosphonic acid;
- 4-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-3-enephosphonic acid;
- 4-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-1-enephosphonic acid;
- 1-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid;
- 2-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid;

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2-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethenephosphonic acid;
4-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-3-enephosphonic acid, and
4-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-1-enephosphonic acid.

Example 14: Tablets, each comprising 50 mg of 2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid or a salt, for example the sodium salt, thereof can be prepared as follows:

Composition (10 000 tablets)

active ingredient	500.0 g
lactose	500.0 g
potato starch	
gelatin	8.0 g
talc	60.0 g
magnesium stearate	10.0 g
silicon dioxide (highly dispersed)	20.0 g
ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of the potato starch, and the mixture is moistened with an ethanolic solution of the gelatin and granulated through a sieve. After drying, the remainder of the potato starch, the magnesium stearate, the talc and the silicon dioxide are mixed in and the mixture is compressed to form tablets each weighing 145.0 mg and comprising 50 mg of active ingredient; if desired, the tablets may be provided with dividing notches for finer adaptation of the dose.

Example 15: A sterile-filtered aqueous gelatin solution with 20 % cyclodextrins as solubiliser, comprising 3 mg each of 2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid or a salt, for example the sodium salt, thereof as active ingredient, is mixed with a sterile gelatin solution containing phenol as preservative, with heating and under aseptic conditions, in such a manner that 1.0 ml of solution has the following composition:

active ingredient	3 mg
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gelatin	150.0 mg
phenol	4.7 mg
dist. water with 20 % cyclodextrins as solubiliser	1.0 ml

Example 16: For the preparation of a sterile dry substance for injection comprising 5 mg each of 2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid or a salt, for example the sodium salt, thereof, 5 mg of one of the compounds of formula I mentioned in the preceding Examples, as active ingredient, are dissolved in 1 ml of an aqueous solution with 20 mg of mannitol and 20 % cyclodextrins as solubiliser. The solution is sterile-filtered and, under aseptic conditions, introduced into a 2 ml ampoule, deep-frozen and lyophilised. Before use, the lyophilisate is dissolved in 1 ml of distilled water or 1 ml of physiological sodium chloride solution. The solution is administered intramuscularly or intravenously. The formulation can also be introduced into double-chamber disposable syringes.

Example 17: 10 000 film-coated tablets, each comprising 100 mg of 2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid or a salt, for example the sodium salt, thereof, can be prepared as follows:

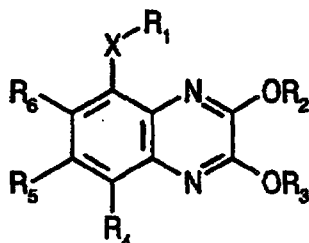
active ingredient	1000 g
corn starch	680 g
colloidal silica	200 g
magnesium stearate	20 g
stearic acid	50 g
sodium carboxymethyl starch	250 g
water	q. s.

A mixture of one of the compounds of formula I mentioned in the preceding Examples, as active ingredient, 50 g of corn starch and the colloidal silica is made into a moist mass with a starch paste prepared from 250 g of corn starch and 2.2 kg of demineralised water. The moist mass is forced through a sieve of 3 mm mesh size and dried in a fluidised bed drier at 45° for 30 minutes. The dry granules are pressed through a sieve of 1 mm mesh size, mixed with a previously sieved mixture (1 mm sieve) of 330 g of corn starch, the magnesium stearate, the stearic acid and the sodium carboxymethyl starch and compressed to form slightly domed tablets.

Example 18: In a manner analogous to that described in Examples 14 to 17 it is also possible to prepare pharmaceutical compositions comprising a different compound according to any one of Examples 1 to 13.

What is claimed is:

1. A novel quinoxaline- or quinoxaliny-alkanephosphonic acid of formula I



(I)

wherein

R_1 is free or partially esterified phosphono,

R_2 and R_3 are each independently of the other hydrogen or an aliphatic radical, the radicals R_4 , R_5 and R_6 are each independently of the others hydrogen, an aliphatic hydrocarbon radical, free or etherified hydroxy, free or etherified mercapto or oxidised free or etherified mercapto, unsubstituted or aliphatically substituted amino, nitro, free or esterified or amidated carboxy, cyano, free or amidated sulfamoyl, halogen or trifluoromethyl, and

X is a divalent aliphatic radical,

or a tautomer thereof, or in each case a salt thereof.

2. A compound according to claim 1 of formula I wherein

R_1 is phosphono or lower alkylphosphono,

R_2 and R_3 are each independently of the other hydrogen, lower alkyl, lower alkenyl or lower alkynyl, such as propargyl,

the radicals R_4 , R_5 and R_6 are each independently of the others hydrogen, lower alkyl, lower alkenyl, lower alkynyl, hydroxy, lower alkoxy, lower alkenyloxy, lower alkynyloxy, mercapto, lower alkylthio, lower alkanesulfinyl, lower alkanesulfonyl, lower alkenylthio, lower alkynylthio, lower alkenesulfinyl, lower alkanesulfonyl, amino, lower alkylamino, di-lower alkylamino, nitro, carboxy, lower alkoxycarbonyl; unsubstituted or lower alkyl-, lower alkoxy-, hydroxy-, halo- and/or trifluoromethyl-substituted phenyl-lower alkoxycarbonyl; carbamoyl, lower alkylcarbamoyl, di-lower alkylcarbamoyl; phenylcarbamoyl or N-phenyl-N-lower alkylcarbamoyl, each of which is unsubstituted or substituted in the phenyl moiety by lower



alkyl, lower alkoxy, hydroxy, halogen and/or by trifluoromethyl; cyano, phosphono, lower alkylphosphono, di-lower alkylphosphono, halogen or trifluoromethyl, and X is lower alkylidene, lower alkylene, lower alkenylene or lower alkynylene, or a tautomer thereof, or in each case a salt thereof.

3. A compound according to claim 1 of formula I wherein

R₁ is phosphono,

R₂ and R₃ are each independently of the other hydrogen or C₁-C₄alkyl, such as methyl or ethyl,

the radicals R₄, R₅ and R₆ are each independently of the others hydrogen, C₁-C₄alkyl, such as methyl or ethyl, C₁-C₄alkoxy, such as methoxy or ethoxy, C₁-C₄alkylthio, such as methylthio, amino, nitro, carboxy, C₁-C₄alkoxycarbonyl, such as methoxy- or ethoxy-carbonyl, carbamoyl, C₁-C₄alkylcarbamoyl, such as methylcarbamoyl, di-C₁-C₄alkylcarbamoyl, such as dimethylcarbamoyl, halogen or trifluoromethyl, and

X is C₁-C₄alkylidene, such as methylene, ethylidene, 1,1- or 2,2-propylidene or 1,1- or 2,2-butylidene,

or a tautomer thereof, or in each case a salt thereof.

4. A compound according to claim 1 of formula I wherein

R₁ is phosphono,

R₂ and R₃ are each independently of the other hydrogen or C₁-C₄alkyl, such as methyl or ethyl,

the radicals R₄, R₅ and R₆ are each independently of the others hydrogen, C₁-C₄alkyl, such as methyl or ethyl, C₁-C₄alkoxy, such as methoxy or ethoxy, C₁-C₄alkylthio, such as methylthio, amino, nitro, carboxy, C₁-C₄alkoxycarbonyl, such as methoxy- or ethoxy-carbonyl, carbamoyl, C₁-C₄alkylcarbamoyl, such as methylcarbamoyl, di-C₁-C₄alkylcarbamoyl, such as dimethylcarbamoyl, halogen or trifluoromethyl, and

X is C₁-C₄alkylidene, C₁-C₄alkylene, C₂-C₄alkenylene or C₂-C₄alkynylene, or a tautomer thereof, or in each case a salt thereof.

5. 7-Bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid;

2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid;

7-bromo-6-nitro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid;



1-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid or 7-bromo-3-methoxy-2-oxo-1,2,3,4-tetrahydro-quinoxalin-5-ylmethanephosphonic acid or in each case a salt thereof.

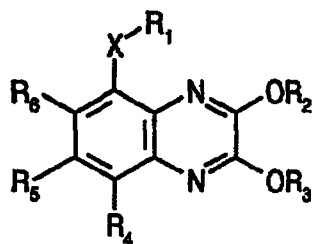
6. 3-(7-Chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)propanephosphonic acid;
3-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-ynephosphonic acid;
3-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-enephosphonic acid;
2-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethenephosphonic acid;
2-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid;
4-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)butanephosphonic acid;
1-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid;
2-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid;
3-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)propanephosphonic acid;
4-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)butanephosphonic acid;
4-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-1-enephosphonic acid;
4-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-3-enephosphonic acid;
2-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethenephosphonic acid;
3-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-enephosphonic acid;
3-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-ynephosphonic acid;
4-(2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-3-enephosphonic acid;
3-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)propanephosphonic acid;
4-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)butanephosphonic acid;
3-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-enephosphonic acid;
3-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)prop-2-ynephosphonic acid;
4-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-3-enephosphonic acid;
4-(7-bromo-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-1-enephosphonic acid;
1-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid;
2-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethanephosphonic acid;
2-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)ethenephosphonic acid;
4-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-3-enephosphonic acid or
4-(7-chloro-2,3-dioxo-1,2,3,4-tetrahydro-quinoxalin-5-yl)but-1-enephosphonic acid,
or in each case a salt thereof.



7. A compound according to any one of claims 1 to 6 for the therapeutic treatment of the human or animal body.

8. A pharmaceutical composition comprising a compound according to any one of claims 1 to 7 in free form or in the form of a pharmaceutically acceptable salt, together with customary pharmaceutical excipients.

9. A process for the preparation of a novel quinoxaline- or quinoxaliny-alkanephosphonic acid of formula I



(I)

wherein

R_1 is free or partially esterified phosphono,

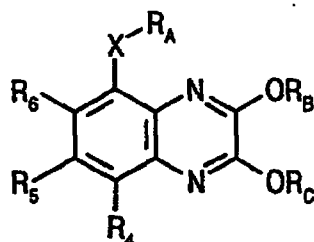
R_2 and R_3 are each independently of the other hydrogen or an aliphatic radical, the radicals R_4 , R_5 and R_6 are each independently of the others hydrogen, an aliphatic hydrocarbon radical, free or etherified hydroxy, free or etherified mercapto or oxidised free or etherified mercapto, unsubstituted or aliphatically substituted amino, nitro, free or esterified or amidated carboxy, cyano, free or amidated sulfamoyl, halogen or trifluoromethyl, and

X is a divalent aliphatic radical,

or a tautomer thereof, or in each case a salt thereof,

which process comprises

removing the phosphono-protecting group, and, if desired, the group R_B and/or R_C , from a compound of formula II

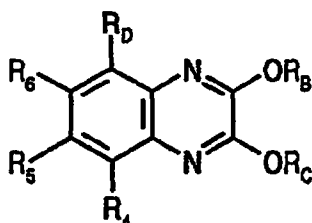


(II),

wherein R_A is a protected phosphono group, R_B is a group R_2 or a hydroxy-protecting group, R_C is a group R_3 or a hydroxy-protecting group, and R_4 , R_5 and R_6 are as defined, and if desired converting the resulting compound into a different compound of formula I, separating a mixture of isomers obtainable according to the process into its components and isolating the particular preferred isomer and/or converting a free compound obtainable according to the process into a salt or converting a salt obtainable according to the process into the corresponding free compound.

10. A method of treating pathological conditions that are responsive to blocking of NMDA-sensitive receptors, for example ischaemic disorders, such as cerebral ischaemia and ischaemic disorders of the eyes, vascular and muscular spasms, such as migraine or local or general spasticity, and especially convulsions, such as epilepsy, which method comprises administering a compound according to claim 1.

11. A compound of formula XVII



(XVII)

wherein

the radicals R_4 , R_5 and R_6 are each independently of the others hydrogen, an aliphatic hydrocarbon radical, free or etherified hydroxy, free or etherified mercapto or oxidised free or etherified mercapto, unsubstituted or aliphatically substituted amino, nitro, free or esterified or amidated carboxy, cyano, free or amidated sulfamoyl, halogen or trifluoromethyl,



R_B is a group R_2 or a hydroxy-protecting group, R_C is a group R_3 or a hydroxy-protecting group and

R_D is a group of the formula

$-(CH_2)_n-R_E$ (XVIIa), $-(CH_2)_{n-1}-CH=O$ (XVIIb), $-C\equiv C-(CH_2)_{n-2}-R_E$ (XVIIc),

$-C\equiv C-(CH_2)_{n-2}-CH=O$ (XVIIId), $-CH=CH-(CH_2)_{n-2}-R_E$ (XVIIe) or

$-CH=CH-(CH_2)_{n-2}-CH=O$ (XVIIIf)

wherein R_E is free or reactive esterified hydroxy,

and n is 2, 3 or 4,

and the use thereof as an intermediate.