

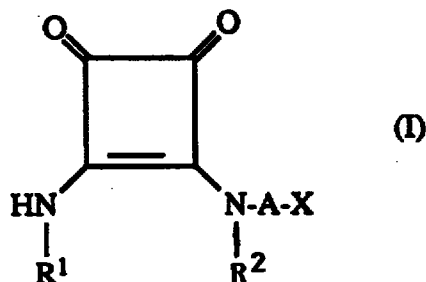
Description

Excitatory amino acids such as glutamic acid have been shown to be important neurotransmitters (Johnson, R.L.; Koerner, J.F., *J. Med. Chem.* 1988, 31, 2057), which in excess participate in the sequence of events leading to neuronal damage after cerebral ischemia (Choi, D.W., *Trends Neurosci.* 1988, 11, 485). One important subtype of excitatory amino acid receptor is the NMDA-receptor, which is defined by the selective agonist N-methyl-D-aspartic acid (NMDA). Blocking the action of endogenous agonist by the selective NMDA-receptor antagonist 4-(3-phosphonopropyl)-2-piperazinecarboxylic acid (CPP) has been shown to prevent ischemic brain damage in gerbils (Boast, C.A. *et al.*, *Brain Research*, 1988, 442, 345). Also, NMDA-induced convulsions have been prevented by CPP in mice (Lehmann, J. *et al.*, *J. Pharmacol. Exp. Ther.* 1987, 240, 737). Finally, competitive NMDA antagonists such as CPP have been shown to prevent the Parkinsonian-like symptoms induced by MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) in rats (Turski, L. *et al.*, *Nature* 1991, 349, 414). For these reasons, NMDA-receptor antagonists are considered appropriate for treatment of epilepsy, stroke (Engelsen, B., *Acta. Neurol Scand.* 1986, 74, 337), and neurodegenerative disorders such as Alzheimer's disease (Maragos, W.F. *et al.*, *Trends Neurosci.* 1987, 10, 65) and Parkinson's disease.

Chemical entities known to be competitive NMDA-receptor antagonists contain the α -amino-carboxylic acid and phosphonic acid functionalities separated by a variety of spacer units. An unembellished example is 2-amino-5-phosphonovaleric acid (AP5) (Watkins, J.C.; Evans, R.H., *Annu. Rev. Pharmacol. Toxicol.* 1981, 21, 165), which contains a saturated carbon chain. More complex examples, which contain elements enhancing structural rigidity and therefore potency, include CPP (see above), cis-4-(phosphonomethyl)-2-piperidinecarboxylic acid (CGS-19755) (Lehman, J. *et al.*, *J. Pharmacol. Exp. Ther.* 1988, 246, 65), and (E)-2-amino-4-methyl-5-phosphono-3-pentenoic acid (CGP-37849) (Schmutz, M. *et al.*, *Abs. Soc. Neurosci.* 1988, 14, 864). Although there has been effort to find groups which are bioisosteric with the phosphonic acid group (Chenard, B.L. *et al.*, *J. Med Chem.* 1990, 33, 1077), no examples of NMDA-receptor antagonists have appeared in the literature which demonstrate a bioisosteric replacement of the α -aminocarboxylic acid functionality.

In accordance with this invention, there is provided a group of N-substituted 3,4-diamino-3-cyclobutene-1,2-dione derivatives which are NMDA antagonists which are recognized by the correct receptors and which prevent NMDA-induced lethality *in vivo*.

Useful as anticonvulsants and neuroprotectants in situations involving excessive release of excitatory amino acids, the compounds of this invention present the following structural formula (I):



in which

R¹ is hydrogen, alkyl of 1 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms;

R² is hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms;

or

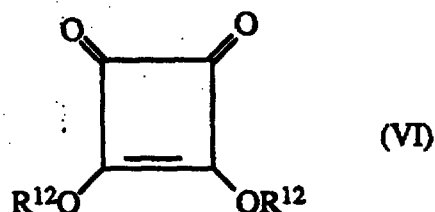
R¹ and R² taken together are Z, which is -CH₂CH₂-, -CH₂C(R⁵)(R⁷)CH₂- or -CH₂C(R⁸)(R⁹)-C(R¹⁰)-(R¹¹)CH₂-, where R⁵, R⁸ and R¹⁰ are, independently, hydrogen, alkyl of 1 to 6 carbon atoms or hydroxyl and R⁷, R⁹ and R¹¹ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms;

A is alkylene of 1 to 6 carbon atoms or alkenylene of 2 to 6 carbon atoms;

X is CO₂R³ in which R³ is hydrogen or alkyl of 1 to 6 carbon atoms, P(O)(OR⁴)(OR⁵) in which R⁴ and R⁵ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms, 3,5-dioxo-1,2,4-oxadiazolidin-2-yl or 5-tetrazolyl;

wherein R^1 is as defined above and removing any protecting group to give a corresponding compound of formula (I) or a salt thereof; or

c) reacting a compound of formula (VI):

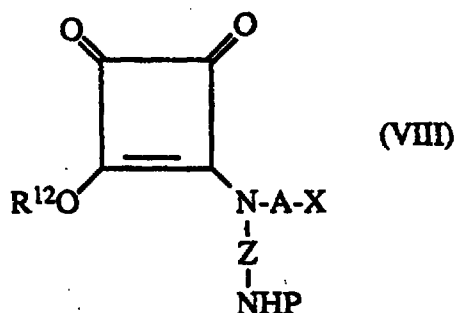


wherein R^{12} is as defined above and each is the same or different, with a compound of formula:



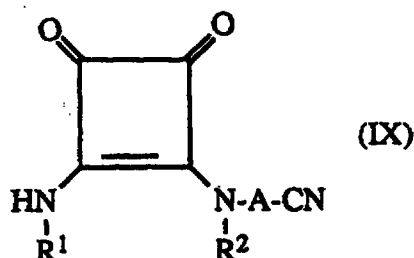
wherein X is as defined above or a salt or protected form thereof, Z and A are as defined above, if required removing any protecting group to give a corresponding compound having formula (I) wherein R^1 and R^2 taken together are Z, A and X are as defined above; or

d) deprotecting, selectively if required, and cyclising a compound of the formula (VIII):



wherein X, Z, R^{12} and A are as defined above or X may be -CN or a salt or protected form thereof, and P is an amino protecting group, which is preferably selectively removable if X is protected to give a corresponding compound having formula (I) where R^1 and R^2 are Z, if required also removing any protecting group on X; or

e) reacting a compound of the formula (IX):



wherein R^1 , R^2 and A are as defined above, with an azide, such as an alkali metal azide, e.g. NaN_3 or tributyltin azide to give a corresponding compound of formula (I) where X is 5-tetrazolyl; or

f) converting a compound of formula (I) wherein R^3 , R^4 and R^5 are alkyl groups to give compounds of the formula (I) wherein R^3 , R^4 and R^5 are hydrogen or salts thereof; or

g) acidifying a salt of a compound of formula (I) to give the free acid or basifying an acid of formula (I) to give a salt thereof; or

or a pharmaceutically acceptable salt thereof.

Examples of alkyl for R^{1-5} and R^{6-16} , infra, are straight or branched groups such as methyl, ethyl, n-propyl, isopropyl, butyl and hexyl. Preferred alkyl groups have 1 to 4 carbon atoms. Examples of alkenyl for R^2 are straight or branched groups such as vinyl, prop-1-enyl, alkyl, methallyl, but-1-enyl, but-2-enyl and but-3-enyl.

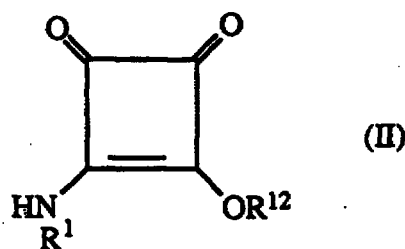
Examples of phenylalkyl groups for R^1 and R^2 are such groups wherein the alkyl moiety is a straight or branched chain such as benzyl, phenethyl, 3-phenylpropyl, 4-phenyl butyl. Preferably the alkyl moiety of such a group contains 1 to 4 carbon atoms.

Preferred values for R^1 and R^2 are, independently, hydrogen, methyl, allyl, methallyl and benzyl, and when R^1 and R^2 are taken together as Z, they are $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{R}^5)(\text{R}^7)\text{CH}_2-$ or $-\text{CH}_2\text{C}(\text{R}^8)(\text{R}^9)-\text{C}(\text{R}^{10})(\text{R}^{11})\text{CH}_2-$, where R^5 , R^8 and R^{10} are, independently, hydrogen, alkyl of 1 to 6 carbon atoms or hydroxyl and R^7 , R^9 and R^{11} are, independently, hydrogen or alkyl of 1 to 6 carbon atoms. Examples of alkylene groups for A are straight or branched chain groups preferably those having 1 to 4 carbon atoms such as: $-\text{CH}_2-$, $-\text{CH}_2\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2\text{CH}(\text{CH}_3)-$, $-(\text{CH}_2)_3-$ and $-(\text{CH}_2)_4-$. Examples of alkenylene groups for A are cis and trans groups preferably having 2 to 4 carbon atoms such as $-\text{CH}_2-\text{CH}=\text{CH}-$, $-\text{CH}=\text{C}(\text{CH}_3)-$, $-\text{C}(\text{CH}_3)=\text{CH}-$, $-\text{CH}=\text{CH}-\text{CH}_2-$ and $-\text{CH}_2-\text{CH}=\text{CH}-\text{CH}_2-$ and $-\text{CH}_2-\text{CH}=\text{C}(\text{CH}_3)-$. Preferably A is alkylene of 1 to 4 carbon atoms or trans -2-butylene. Preferred values for X are carboxyl, phosphonyl or 5-tetrazolyl.

The pharmaceutically acceptable, salts of the compounds of this invention include the alkali metal (sodium, potassium or lithium), alkaline earth metal (calcium or magnesium) and ammonium salts.

This invention also provides processes for preparing the compounds of formula (I).

Accordingly, this invention provides a process for preparing a compound of formula I which comprises:
a) reacting a compound of formula (II):

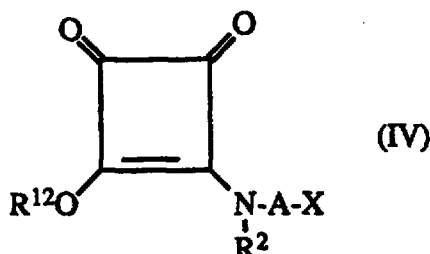


wherein R^1 is as defined above and OR^{12} represents any alkoxy or aralkoxy leaving groups such as those having 1 to 6 and 7 to 12 carbon atoms, respectively, e.g. methoxy, ethoxy, benzyloxy, with a compound of formula (III):



wherein R^2 , A and X are as defined above or a salt or protected form thereof, if required removing any protecting group to give a compound of formula (I) wherein R^2 is as defined above if desired isolating as a pharmaceutically acceptable salt;

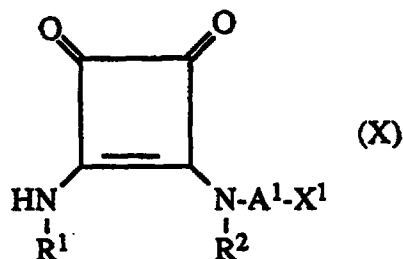
b) reacting a compound of formula (IV):



wherein X, R^2 and R^{12} are as defined above or a salt or protected form thereof with a compound of formula:



h) thermolysing a compound of the formula (X)



wherein R¹ is defined above, X¹ is CO₂R³ or -PO(OR⁴)(OR⁵) where R³, R⁴ and R⁵ are all alkyl, 3,5-dioxo-1,2,4-oxadiazolidin-2-yl or protected 5-tetrazolyl, and -A¹- represents alkylene of 2 to 6 carbon atoms substituted by a-S(O)ₘ-aryl radical where m represents 1 or 2, if required removing any protecting group to give a corresponding compound of formula (I) wherein A is alkenylene of 2 to 6 carbon atoms. Examples of aryl are univalent, aromatic hydrocarbons preferably having 7 to 12 carbon atoms, e.g. phenyl, tolyl, and the like.

As will be apparent to those skilled in the art, in some of the above mentioned reactions, where it is desired to prepare X as a carboxy or phosphonic acid, it may be necessary or advisable to protect such groups during the reaction or use a C₁-C₆ alkyl ester derivative thereof, e.g. t-butyl ester, followed by its removal. Examples of carboxy protecting groups are benzyl esters or esters of 7 or more carbon atoms.

Similarly, when X is 5-tetrazolyl, this group may be protected by standard means, e.g. using a trityl protecting group which is removable by acidification or hydrogenation. In addition, when R⁶, R⁸ or R¹⁰ are hydroxy, appropriate protection during the reaction may be effected with the acetyl, benzoyl, t-butyl, trityl, and preferably the benzyl group.

With regard to process a), the displacement of an alkoxy or aralkoxy substituent from the compound of formula (II) may be conveniently carried out in the absence of presence of base such as an alkali metal hydroxide (e.g. NaOH) with or without heating in the presence of an inert solvent such as ethanol. When X is an acidic moiety in the compound of formula (III) under basic reaction conditions, the product will be a salt which can be isolated as such or converted to the free acid by acidification. When X is a carboxylic acid function it may be protected, e.g. in the form of an ester or as a salt with a cation.

With regard to process b), the displacement of the OR¹² group may be carried out using ammonia or an amine of formula H₂NR² in the presence of an inert solvent such as ethanol with or without heating, the group X being protected if required.

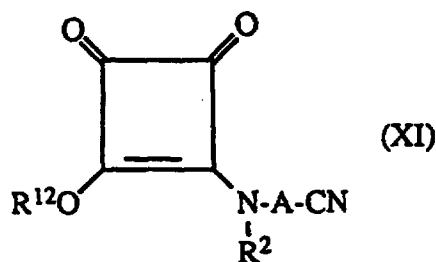
With regard to process c), bicyclic compounds of formula I may be prepared by carrying out two displacement reactions using a diamine of formula VII preferably by heating in an inert solvent such as ethanol. If the nitrogen is protected, the reaction may be carried out in two steps via an intermediate of formula (VIII) followed by deprotection and cyclisation as described in process d). Examples of amino protecting groups are benzyloxycarbonyl and substituent derivatives thereof removable by hydrogenation.

Process e) may be carried out using an alkali metal azide in an inert solvent such as dimethyl formamide in the presence of ammonium chloride with heating if necessary. When tributyltin azide is used, then the reaction may be carried out in an inert solvent such as toluene followed by acidification.

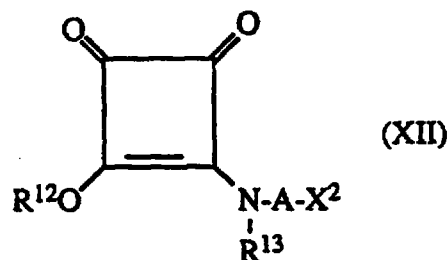
With regard to process f), when any of R³ or R⁴ and R⁵ are alkyl groups, these may be removed by hydrolysis or other known methods to give the corresponding free acids or salts thereof.

Thermolysis of the compounds of formula X may be carried out by heating in an inert high boiling solvent such as toluene in the presence of sodium bicarbonate in order to produce compounds of formula I where A is alkenylene. Similarly, this process may be used to prepare starting materials used in the processes above where it is desired to prepare compounds wherein A represents alkenylene.

This invention also provides intermediates for preparing compounds of the formula (I). These intermediates include compounds having formulae (IV), (VIII) as shown and defined hereinabove and also intermediates to compounds of formula (IX) which intermediates having the formula (XI):



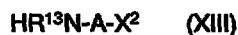
The intermediates may be represented by the single general formula (XII):



or a salt thereof,

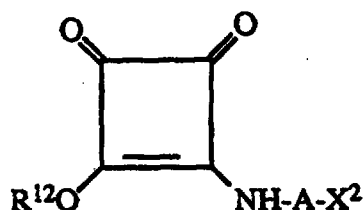
where X^2 represents CN, $COOR^{14}$ where R^{14} is hydrogen, alkyl of 1 to 6 carbon atoms or a carboxyl protecting group, $-PO(OR^{15})(OR^{16})$ where R^{15} and R^{16} are hydrogen or alkyl of 1 to 6 carbon atoms, 3,5-dioxo-1,2,4-oxadiazolidinyl or optionally protected 5-tetrazolyl, R^{12} and A are as defined above, and R^{13} represents hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, phenylalkyl of 7 to 12 carbon atoms or -Z-NHP wherein, P is an amino protecting group and Z is hereinbefore defined.

Also included in this invention is a process for preparing the intermediates of formula (XII) which process comprises reacting a compound of formula (VI) as defined above, with a compound of the formula:



where A, R^{13} and X^2 are as defined above, to give a corresponding compound of the formula (XII),

or N-alkylating a compound of formula:



XIV

where R^{12} , A and X^2 are as defined above in the presence of a strong base, e.g. NaH, with a compound of formula R^2 -halo where halo is a halogen such as chlorine or bromine and R^2 is as defined above except hydrogen to give a corresponding compound of formula (XII).

Starting materials used in any of the above mentioned processes for preparing the final products and intermediates are known compounds or can be prepared by analogous methods for known compounds.

The compounds of this invention are produced by conventional methods involving (1) the displacement of the alkoxy substituent of 3-amino-4-alkoxy-3-cyclobutene-1,2-dione with an amino acid (H_2NAX) in the presence of an equivalent weight of sodium hydroxide to obtain derivatives in which R^2 is hydrogen; (2) reacting 3,4-dialkoxy-3-cyclobutene-1,2-dione with an amine (H_2NR^2) followed by N-alkylation with the desired t-butylhalocarboxylate (halo ACO_2 -t-butyl) in dimethyl formamide employing sodium hydride as the base, followed by displacement of the remaining alkoxy substituent with the desired amine (H_2NR^1) and

deprotection of the *t*-butyl ester with an acid such as formic acid; and (3) in an analogous manner, 3,4-dialkoxy-3-cyclobutene-1,2-dione may be reacted with the desired amino acid ($\text{H}_2\text{N-A-PO}_3\text{Et}_2$) to displace one alkoxy group, and that intermediate may be N-alkylated in dimethylformamide with the desired alkyl halide (R^2 halo) in the presence of sodium hydride and/or the other alkoxy substituent can be displaced with the desired amine (H_2NR^1). The resulting phosphonate ester is converted to the free acid with bromotrimethylsilane. Employing a diamine such as $\text{H}_2\text{N-(CH}_2)_n\text{-NHCH}_2\text{CH}_2\text{PO}_3\text{Et}_2$ ($n=2-4$) with 3,4-diethoxy-3-cyclobutene-1,2-dione affords the dioxodiazabicycloethyl phosphonic acid esters such as is illustrated in Example 7, *infra*. The phosphonate ester is converted to the free acid conventionally. The initial diamine reactants are prepared by reacting N-protected alkylene diamines with (2-oxoethyl)phosphonic acid diethyl ester in the presence of sodium cyanoborohydride in methanol at a pH ~6.5 followed by removal of the N-protecting group, such as benzyloxycarbonyl, by hydrogenation.

Also, (4) the initial mono protected diamine phosphonate reactants are prepared by reacting N-protected alkylene diamines with $\text{Br-A-PO}_3\text{Et}_2$ in the presence of sodium carbonate in ethanol. The monoprotected diamine phosphonate such as (protecting group)- $\text{NH-(CH}_2)_n\text{-NH-A-PO}_3\text{Et}_2$ ($n=2-4$) is reacted with 3,4-dialkoxy-3-cyclobutene-1,2-dione to displace one alkoxy group. Removal of the benzyloxycarbonyl N-protecting group by hydrogenation or the *t*-butyloxycarbonyl N-protecting group by formic acid treatment leads to cyclization. The resulting dioxodiazabicycloalkylphosphonic acid esters are hydrolyzed to the free acid with bromotrimethylsilane; (5) the mono N-benzyloxycarbonyl diamine may be alkylated with $\text{Br-A-CO}_2\text{-t-Bu}$ in the presence of diisopropylethylamine in dimethylformamide. The intermediate $\text{CBZ-NH-(CH}_2)_n\text{-NH-A-CO}_2\text{-t-Bu}$ is reacted with 3,4-dialkoxy-3-cyclobutene-1,2-dione to displace one alkoxy group. Removal of the N-protecting group by hydrogenation of the intermediate leads to cyclization. The *t*-butyl group is cleaved by formic acid treatment to give the free acid; and (6) the mono N-*t*-butyloxycarbonyl diamine may be alkylated with Br-A-CN in the conventional manner. The intermediate $\text{BOC-NH-(CH}_2)_n\text{-NH-A-CN}$ is reacted with 3,4-dialkoxy-3-cyclobutene-1,2-dione to displace one alkoxy group. Removal of the N-protecting group by formic acid treatment leads to cyclization. The nitrile is converted to the tetrazole by heating with sodium azide and ammonium chloride in dimethylformamide. When the alkylene bridge of the diamine contains a hydroxyl group, it is optionally O-protected throughout the reaction.

In all of the above reactions, the reactants are either known, commercially available or readily prepared by methods well within the skill of the medicinal chemist.

The compounds of the invention may contain one or more asymmetric carbon atoms (e.g. when any of $\text{R}^6\text{-}^{10}$ is alkyl or any of R^6 , R^8 and R^{10} is hydroxyl), so that the compounds can exist in different stereoisomeric forms. All stereoisomeric forms are included within the invention. Such compounds can be, for example, racemates of optically active forms. The optically active forms can be obtained by resolution of the racemates or by asymmetric synthesis.

The following examples illustrate, without limitation, the preparation of representative compounds of this invention:

Example 1

N-(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)beta-alanine

A solution of 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (2.0 g, 14 mmol) in ethanol (100 mL) was treated with β -alanine (1.26 g, 14 mmol) dissolved in 1 N sodium hydroxide solution (14 mL, 14 mmol). After 5.5 hours at room temperature, the resulting yellow solid was filtered, washed with ethanol, and concentrated under high vacuum to yield the pure title compound as the sodium salt, hemihydrate (2.6 g, 86% of theory, m.p. 280-282°C); IR (KBr, cm^{-1}): 1810; MS (-FAB) 205 (M-H, 13) 183 (M-Na, 44), 175 (17), 148 (100); ^1H NMR (D_2O , 400 MHz): δ 3.59 (br s, 2H), 2.31 (t, $J = 6$ Hz, 2H); ^{13}C NMR (D_2O , 400 MHz): ppm 182.01, 181.61, 179.30, 168.94, 168.54, 41.18, 37.97.

Elemental analysis for $\text{C}_7\text{H}_7\text{NaN}_2\text{O}_4 \cdot 1/2 \text{H}_2\text{O}$			
Calc'd:	C, 39.08;	H, 3.75;	N, 13.02
Found:	C, 38.78;	H, 3.48;	N, 12.86

a) In the same manner, condensing stoichiometric amounts of 3-amino-4-ethoxy-3-cyclobutene-1,2-dione with ethyl glycinate produces N-(2-amino-3,4-dioxo-1-cyclobutenyl)glycine ethyl ester, m.p. 231-233°C.

Elemental analysis for $C_8H_{10}N_2O_4$			
Calc'd:	C, 48.49;	H, 5.09;	N, 14.14
Found:	C, 48.40;	H, 4.90;	N, 14.02

b) The substitution of glycine for β -alanine in the procedure of Example 1 yields N-(2-amino-3,4-dioxo-1-cyclobutenyl)glycine as the sodium salt, $4/3 H_2O$, m.p. 210-215 °C (dec.).

Elemental analysis for $C_6H_5NaN_2O_4 \cdot 4/3 H_2O$			
Calc'd:	C, 33.34;	H, 3.58;	N, 12.96
Found:	C, 33.36;	H, 3.26;	N, 13.12

c) Similarly, the substitution of 4-aminobutanoic acid for β -alanine in the procedure of Example 1 affords 4-[(2-amino-3,4-dioxo-1-cyclobutenyl)amino]butanoic acid as the sodium salt, partial hydrate, m.p. 240-243 °C (dec.).

Elemental analysis for $C_8H_9NaN_2O_4 \cdot 0.58 H_2O$			
Calc'd:	C, 41.67;	H, 4.44;	N, 12.15
Found:	C, 41.27;	H, 4.04;	N, 12.03

Example 2

2-[2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]-1,2,4-oxadiazolidine-3,5-dione

A solution of 3-amino-4-ethoxy-3-cyclobutene-1,2-dione (0.56 g, 4.0 mmol) in ethanol (20 mL) was added to 2-(2-aminoethyl)-1,2,4-oxadiazolidine-3,5-dione hydrobromide (0.90 g, 4.0 mmol) in ethanol (100 mL). The reaction mixture was treated with 1N sodium hydroxide solution (8 mL, 8 mmol) and allowed to stir for 24 hours at room temperature. The resulting precipitate was filtered, dissolved in water and passed through an ion exchange column (AG 50W-X2, 100-200 mesh, H^+ form), eluting with water. The eluent was freeze dried yielding the title compound as a cream colored solid, partial hydrate (0.45 g, 45%, mp 225 °C (dec)); IR (KBr, cm^{-1}) 3300, 3140, 1820, 1740, 1720, 1640; MS (+FAB) 241 (MH^+); 1H NMR (DMSO, 400 MHz): δ 12.4 (br s, NH), 7.5 (br s, 3 NH), 4.0-3.5 (m, 4H); ^{13}C NMR (DMSO, 400 MHz): ppm 183.72, 183.63, 170.06, 168.96, 158.17, 152.72, 50.41, 41.68.

Elemental analysis for $C_8H_9NaO_5 \cdot 0.45 H_2O$			
Calc'd:	C, 38.70;	H, 3.61;	N, 22.56
Found:	C, 39.10;	H, 3.24;	N, 22.19

a) The same reaction conditions as illustrated in Examples 1 and 2 applied to β -alanine and 4-ethoxy-3-methylamino-3-cyclobutene-1,2-dione provides N-[2-(methylamino)-3,4-dioxo-1-cyclobutenyl] β -alanine as the sodium salt, $1/4 H_2O$, m.p. 310 °C (dec.).

Elemental analysis for $C_8H_9NaN_2O_4 \cdot 1/4 H_2O$			
Calc'd:	C, 42.77;	H, 4.26;	N, 12.47
Found:	C, 42.77;	H, 3.88;	N, 12.53

b) Similarly, 3-benzylamino-4-ethoxy-3-cyclobutene-1,2-dione when reacted with β -alanine produces 3-[[3,4-dioxo-2[(phenylmethyl)amino]-1-cyclobutenyl]amino]propanoic acid as the sodium salt, $1/2 H_2O$, m.p. 298-302 °C (dec.).

Elemental analysis for $C_{14}H_{13}NaN_2O_4 \cdot 1/2 H_2O$			
Calc'd:	C, 55.08;	H, 4.62;	N, 9.18
Found:	C, 54.74;	H, 4.53;	N, 9.06

Example 3**N-(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)glycine**

A solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.2g, 31 mmol) in ethanol (80 mL) was treated at room temperature with allylamine (2.3 mL, 31 mmol), which was dissolved in ethanol (40 mL), over a 2 hour period. The reaction mixture was concentrated in vacuo to afford crude 1-(2-propenylamino)-2-ethoxy-3,4-dioxo-1-cyclobutene as a light yellow solid (5.6 g). The crude intermediate was dissolved in anhydrous dimethylformamide (50 mL) and added dropwise to a suspension of 60% sodium hydride (1.5 g, 37 mmol) in anhydrous dimethylformamide (50 mL) under nitrogen. The anion was quenched with t-butyl bromoacetate (6.0 mL, 37 mmol) and the reaction mixture was stirred for 1.5 hours, poured into water (500 mL), extracted with ethyl acetate (2 x 200 mL), and dried ($MgSO_4$) to yield N-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)glycine 1,1-dimethylethyl ester. Purification was achieved by flash chromatography (10 cm diameter, elution with 20% ethyl acetate in petroleum ether) affording a yellow oil (4.56 g, 50%); 1H NMR ($CDCl_3$, 300 MHz): δ 5.88-5.72 (m, 1H), 5.35-5.22 (m, 2H), 4.80-4.68 (m, 2H), 4.35, 4.08 (d, $J = 7$ Hz, 2H), 4.28, 3.95 (s, 2H), 1.48 (s, 9H), 1.45 (t, $J = 7$ Hz, 3H).

Ethanol ammonia (25 mL) was added to a flask containing N-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)glycine 1,1-dimethylethyl ester (2.5 g, 8.5 mmol) at room temperature. After 5 hours the reaction mixture was concentrated and purified by flash chromatography (5 cm diameter, elution with 5% methanol in dichloromethane) to yield N-(2-amino-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)glycine 1,1-dimethylethyl ester as a white solid (1.6 g, 71%, mp 175-176 °C); IR (KBr, cm^{-1}): 3300, 3140, 1810, 1740, 1670, 1650; MS (EI): 266 (M^+ , 34), 210 (24), 165 (100), 109 (54), 95 (89), 68 (68); 1H NMR (DMSO, 400 MHz): δ 7.70 (br s, NH_2), 5.84-5.77 (m, 1H), 5.26 (d, $J = 17$ Hz, 1H), 5.19 (d, $J = 10$ Hz, 1H), 4.3 - 4.0 (br m, 4H), 1.39 (s, 9H).

Deprotection of N-(2-amino-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)glycine 1,1-dimethyl ethyl ester (1.6, 6.0 mmol) was performed by stirring in formic acid (20 mL) for 24 hours. The reaction mixture was concentrated, azeotroped with dichloromethane and recrystallized with difficulty (oiled out several times) to afford the title compound, 1/4 hydrate, as an off-white solid (0.80 g, 62%, mp 172-175 °C); IR (KBr cm^{-1}): 3330, 3180, 1810, 1720, 1640; MS(EI): 210 (M^+ , 75), 165 (34), 109 (41), 95 (100), 68 (63); 1H NMR (DMSO, 400 MHz): δ 12.94 (br s, OH), 7.70 (s, NH_2), 5.86-5.77 (m, 1H), 5.26 (d, $J = 17$ Hz, 1H), 5.19 (d, $J = 10$ Hz, 1H), 4.3-4.0 (br m, 4H).

Elemental analysis for $C_9H_{10}N_2O_4 \cdot 1/4 H_2O$			
Calc'd:	C, 50.35;	H, 4.93;	N, 13.05
Found:	C, 50.13;	H, 4.82;	N, 12.86

a) Following the procedure of Example 3, with the exception that 2-methylallylamine is employed as the initial reactant, affords N-(2-amino-3,4-dioxo-1-cyclobutenyl)-N-(2-methyl-2-propenyl)glycine, m.p. 184-186 °C.

Elemental analysis for $C_{10}H_{12}N_2O_4 \cdot 0.1 H_2O$			
Calc'd:	C, 53.14;	H, 5.44;	N, 12.39
Found:	C, 53.09;	H, 5.38;	N, 12.16

b) Similarly, employing benzylamine as the initial reactant, the procedure of Example 3 affords N-(2-amino-3,4-dioxo-1-cyclobutenyl)-N-(phenylmethyl)glycine, m.p. 177-179 °C.

Elemental analysis for $C_{13}H_{12}N_2O_4$			
Calc'd:	C, 60.00;	H, 4.65;	N, 10.76
Found:	C, 59.74;	H, 4.60;	N, 10.61

Example 4**[2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid**

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (4.00 g, 23.5 mmol) in ethanol (100 mL) was added 2-aminoethylphosphonic acid diethyl ester (5.43 g, 30.0 mmol) in ethanol (100 mL) over a 1 hour period. After leaving overnight the reaction mixture was preadsorbed onto silica gel and purified by flash chromatography (5.5 cm diameter, gradient elution with 2.5-10% isopropanol in dichloromethane) to yield [2-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid diethyl ester as an oil which solidifies on standing (3.98 g, 55%, mp 66-68 °C); IR (KBr, cm^{-1}): 3400, 3180, 1800, 1700, 1600; MS (+FAB): 306 (MH^+ , 100), 278 (14), 137 (14), 109 (35); 1H NMR ($CDCl_3$, 400 MHz): δ 6.58, 6.46 (br s, NH), 4.75 (br m, 2H), 4.21-4.07 (m, 4H), 4.00, 3.75 (br m, 2H), 2.08 (d of t, J = 17.5 and 6.5 Hz, 2H), 1.46 (br m, 3H), 1.35 (t, J = 7 Hz, 6H).

A solution of [2-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid diethyl ester (1.69 g, 5.5 mmol) in 100% ethanol (40 mL) was placed in flask equipped with an addition funnel and a nitrogen inlet. Saturated ethanolic ammonia (190 mL) was placed in the addition funnel and added dropwise over 1 hour. The reaction mixture was left stirring at room temperature for a total of 24 hours and then concentrated in vacuo. The resulting solid was recrystallized from methanol in ethyl acetate to afford [2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid diethyl ester as a yellow solid (1.27 g, 82%, mp = 150-152 °C dec); IR (KBr, cm^{-1}): 1805, 1650; MS (+FAB): 277 (MH^+ , 100), 182 (20), 109 (15); 1H NMR (DMSO, 400 MHz): δ 7.5 (br s, 3 NH), 4.1-3.9 (m, 4H), 3.7-3.6 (m, 2H), 2.11 (d of t, J = 17.5 and 7.5 Hz, 2H), 1.22 (t, 6H).

Elemental analysis for $C_{10}H_{17}N_2O_5P \cdot 1/5 H_2O$			
Calc'd:	C, 42.92;	H, 6.27;	N, 10.01
Found:	C, 42.90;	H, 6.05;	N, 10.00

A suspension of [2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid diethyl ester one fifth hydrate (0.90 g, 3.2 mmol) in dry 1,2-dichloroethane (47 mL) was placed in a flask which was equipped with a reflux condenser and which had previously been evacuated and placed under nitrogen. Bromotrimethylsilane (2.6 mL, 19.8 mmol) was added to the flask via syringe, and the reaction mixture was refluxed for 10 minutes. The mixture was then concentrated in vacuo to produce a rust colored solid which was dissolved in deionized water (80 mL). The water was washed with diethyl ether (2 x 100 mL) and concentrated in vacuo. The resulting rust colored solid was recrystallized from methanol and water in ethylacetate to produce the title compound as a dark yellow solid (0.360 g, 50%, mp = 230-239 °C dec.); IR (KBr, cm^{-1}): 1790; 1H NMR (DMSO, 400 MHz): δ 7.5 (br s, 3NH), 3.67 (br s, 2H), 1.85 (d of t, J = 17.5 and 7.5 Hz, 2H).

Elemental analysis for $C_5H_9N_2O_5P \cdot 1/5 H_2O$			
Calc'd:	C, 32.21;	H, 4.24;	N, 12.52
Found:	C, 32.20;	H, 4.00;	N, 12.46

a) Following the procedure of Example 4, with the exception that aminomethylphosphonic acid diethyl ester was employed as the reactant, gives [[(2-amino-3,4-dioxo-1-cyclobutenyl)amino]methyl]phosphonic acid as a three quarter hydrate, m.p. 220-250 °C (dec.).

Elemental analysis for $C_5H_7N_2O_5P \cdot 3/4 H_2O$			
Calc'd:	C, 27.35;	H, 3.90;	N, 12.76
Found:	C, 27.72;	H, 3.39;	N, 12.39

b) Again, employing 3-aminopropylphosphonic acid diethyl ester as the reactant in the process of Example 4 gives [3-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]phosphonic acid, m.p. 220-230 °C (dec.).

Elemental analysis for $C_7H_{11}N_2O_5P$			
Calc'd:	C, 35.91;	H, 4.74;	N, 11.96
Found:	C, 35.94;	H, 4.57;	N, 11.76

c) With 4-aminobutylphosphonic acid diethyl ester as the reactant in the process of Example 4, [4-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]phosphonic acid 0.25 hydrate is obtained as the product, m.p. 220-242 °C (dec.).

Elemental analysis for $C_8H_{13}N_2O_5P \cdot 1/4 H_2O$			
Calc'd:	C, 38.03;	H, 5.38;	N, 11.09
Found:	C, 38.09;	H, 5.01;	N, 11.09

Example 5

[(E)-4-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-butenyl]phosphonic acid

A nitrogen blanketed solution of [(E)-4-(N-phthalimido)-2-buten-1-yl]phosphonic acid diethyl ester (8.58 g, 25.4 mmol) prepared by the method of Connel et al., *J. Org. Chem.*, **54**, 3359 (1989) in ethanol (75 mL) was treated with 85% hydrazine hydrate (5 mL) and brought to reflux for 15 minutes. The virtually solid reaction mixture was concentrated and partitioned between 2.5N sodium hydroxide solution (250 mL) and dichloromethane (150 mL) with stirring for 30 minutes. After separating, the aqueous layer was again extracted with dichloromethane (2 x 150 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated to afford [(E)-4-amino-2-buten-1-yl]phosphonic acid diethyl ester (5.32 g, 25 mmol); this material was dissolved in ethanol (100 mL) and added over 1.5 hours to ethanolic (100 mL) 3,4-diethoxy-3-cyclobutene-1,2-dione (4.32 g, 25.4 mmol). After leaving overnight, the reaction mixture was concentrated and purified by flash chromatography (7.5 cm diameter, elution with 3% methanol in dichloromethane) to yield [(E)-4-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-butenyl]phosphonic acid diethyl ester as a light yellow oil (7.15 g, 85%); 1H NMR ($CDCl_3$, 200 MHz): δ 6.5 (br s, NH), 5.75-5.66 (m, 2H), 4.77 (q, J = 7 Hz, 2H), 4.23 (br s, 2H), 4.2-4.0 (m, 4H), 2.61 (d of d, J = 22 and 7 Hz, 2H), 1.46 (t, J = 7 Hz, 3H), 1.33 (t, J = 7 Hz, 6H).

Ethanolic ammonia (235 mL) was combined with [(E)-4-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-butenyl]phosphonic acid diethyl ester (7.15 g, 21.6 mmol) and the solution was left stirring for 3 days and then evaporated. Recrystallization from methanol in ethyl acetate removed a yellow impurity, but flash chromatography (7.5 cm diameter, elution with 5% methanol in dichloromethane) was required to eliminate a more polar contaminant. Recrystallization of this material with methanol in ethyl acetate (final volume = 200 mL) afforded [(E)-4-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-butenyl]phosphonic acid diethyl ester as a flocculant white solid (4.43 g, 68%, mp 145-147 °C); IR (KBr, cm^{-1}): 3280, 3100, 1800, 1640; MS (+FAB): 303 (MH^+ , 100), 135 (62); 1H NMR (DMSO, 400 MHz): δ 7.5 (br s, 3NH), 5.74-5.68 (m, 1H), 5.57-5.48 (m, 1H), 4.09 (br s, 2H), 4.02-3.91 (m, 4H), 2.64 (d of d, J = 21.5 and 7 Hz, 2H), 1.19 (t, J = 7 Hz, 6H).

Elemental analysis for $C_{12}H_{19}N_2O_5P$			
Calc'd:	C, 47.68;	H, 6.34;	N, 9.27
Found:	C, 47.46;	H, 5.95;	N, 9.21

A solution of [(E)-4-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-butenyl]phosphonic acid diethyl ester (1.0 g, 3.3 mmol) and bromotrimethylsilane (4.6 mL, 35 mmol) in anhydrous 1,2-dichloroethane (30 mL) under nitrogen was refluxed for 20 minutes, and then cooled and evaporated. The residue was dissolved in water (150 mL) and washed with diethyl ether (2 x 75 mL). The resulting material, upon concentrating the aqueous layer, was recrystallized from methanol in ethyl acetate (final volume = 100 mL) to yield [(E)-4-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-butenyl]phosphonic acid one third hydrate as a yellow solid (0.59 g, 71%, mp 220-230 °C (dec)); IR (KBr, cm^{-1}): 3280, 3100, 1800, 1640; MS (-FAB): 245 (M-H); 1H NMR (DMSO, 400 MHz): δ 7.47 (br s, 3 NH), 5.63-5.58 (m, 2H), 4.10 (br s, 2H), 2.38 (d of d, J = 21 and 6 Hz, 2H).

Elemental analysis for $C_8H_{11}N_2O_5P \cdot 1/3 H_2O$			
Calc'd:	C, 38.11;	H, 4.66;	N, 11.11
Found:	C, 38.10;	H, 4.46;	N, 11.00

Example 6

[2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid

A cold (0 °C) suspension of 60% sodium hydride (500 mg, 12.5 mmol) in anhydrous dimethylformamide (15 mL) under nitrogen was treated with a solution of [2-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid diethyl ester (3.23 g, 10.6 mmol), prepared as in Example 4, in dimethylformamide (20 mL) over 30 minutes. Iodomethane (0.78 mL, 12.5 mmol) was introduced and the ice bath was removed for 30 minutes and then reapplied for introduction of 1N hydrochloric acid solution (20 mL). The reaction mixture was poured into water (200 mL), extracted with dichloromethane (2 x 200 mL), dried ($MgSO_4$), and concentrated under high vacuum (1 mm) at 40 °C. The crude material was purified by flash chromatography (7.5 cm diameter, elution with 2.5% methanol in dichloromethane) to afford [2-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid diethyl ester as an oil (3.00 g, 89%); IR (neat, cm^{-1}): 1805, 1715, 1620; MS (+FAB): 320 (MH^+ , 100), 109 (20); 1H NMR ($CDCl_3$, 400 MHz): δ 4.78-4.74 (m, 2H), 4.16-4.09 (m, 4H), 3.94, 3.68 (m, 2H), 3.35, 3.19 (s, 3H), 2.15-2.09 (m, 2H), 1.48-1.44 (m, 3H), 1.34 (t, J = 7 Hz, 6H).

An ethanolic solution (40 mL) of [2-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid diethyl ester (3.00 g, 9.40 mmol) was combined with ethanolic ammonia solution (70 mL) and left for 18 hours. After concentrating *in vacuo*, the solid was recrystallized twice from methanol in ethyl acetate (final volume = 50 mL) to yield [2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid diethyl ester as a solid (2.10 g, 77%, mp 130-132 °C); IR (KBr, cm^{-1}): 3320, 3160, 1800, 1670, 1650, 1640; MS (+FAB): 291 (MH^+ , 100), 196 (22), 109 (20); 1H NMR (DMSO, 400 MHz): δ 7.61 (br s NH_2), 4.02 - 3.94 (m, 4H), 3.74 (br s, 2H), 3.13 (br s, 3H), 2.13 (d of t, J = 18 and 7.5 Hz, 2H), 1.22 (t, J = 7 Hz, 6H).

Elemental analysis for $C_{11}H_{19}N_2O_5P$			
Calc'd:	C, 45.52;	H, 6.60;	N, 9.65
Found:	C, 45.41,	H, 6.55,	N, 9.65

A suspension of [2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid diethyl ester (660 mg, 2.3 mmol) in anhydrous 1,2-dichloroethane (20 mL) under nitrogen was treated with bromotrimethylsilane (2.0 mL, 15 mmol) and heated to reflux for 10 minutes. The yellow solution was concentrated and the resulting solid was dissolved in water (75 mL), washed with diethyl ether (2 x 50 mL) and evaporated. The solid was dissolved in boiling methanol, filtered, and concentrated with the addition of ethyl acetate to a final volume of 75 mL to afford the title compound as a yellow solid (310 mg, 58%, mp 230-260 °C dec); IR (KBr, cm^{-1}): 3340, 1800; MS (-FAB): 233 (M-H, 32), 148 (100); 1H NMR (DMSO, 400

MHz): δ 7.62 (br s, NH₂), 3.68 (br s, 2H), 3.16 (br s, 3H), 1.90 (d of t, J = 18 and 7.5 Hz, 2H).

Elemental analysis for C ₇ H ₁₁ N ₂ O ₅ P			
Calc'd:	C, 35.91;	H, 4.74;	N, 11.96
Found:	C, 35.52;	H, 4.79;	N, 11.83

a) Following the procedure in Example 6, with the exception that aminomethylphosphonic acid diethyl ester is employed as the initial reactant gives [[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]-methyl]phosphonic acid, m.p. 245-250 °C (dec.).

Elemental analysis for C ₆ H ₉ N ₂ O ₅ P			
Calc'd:	C, 32.74;	H, 4.12;	N, 12.73
Found:	C, 32.62;	H, 4.15;	N, 12.87

Example 7

[2-(7,8-Dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-yl)ethyl]phosphonic acid

A solution of (2-aminoethyl)carbamic acid phenylmethyl ester (3.06 g, 16 mmol), (2-oxoethyl)phosphonic acid diethyl ester (2.88 g, 16 mmol) and sodium cyanoborohydride (1.00 g, 16 mmol) in dry methanol (90 mL) was prepared under nitrogen. Methanolic hydrogen chloride was added until the solution remained slightly acidic (pH 6.5). After 3 hours, additional sodium cyanoborohydride (0.25 g, 4.0 mmol) was introduced and the reaction was left overnight. After acidifying to pH 1.5 with concentrated hydrochloric acid, the methanol was removed *in vacuo* and the residue was diluted with water (25 mL). After washing with diethyl ether (3 x 25 mL), the aqueous layer was basified to pH 10 with 1 N sodium hydroxide solution, saturated with solid sodium chloride, and then extracted with chloroform (3 x 50 mL). The dried (Na₂SO₄) organic layer was preadsorbed onto silica gel and purified by flash chromatography (3 cm diameter, gradient elution with 5 - 10 % methanol in dichloromethane) to yield [2-[(2-(diethoxyphosphinyl)ethyl)-amino]ethyl]carbamic acid phenylmethyl ester as a pale yellow oil (2.90 g, 51 %); IR (neat, cm⁻¹): 3300, 1715; MS (+FAB): 359 (MH⁺, 100), 91 (70); ¹H NMR (CDCl₃, 400 MHz): δ 7.36 (m, 5H), 5.46 (br s, NH), 5.10 (s, 2H), 4.16 - 4.02 (m, 4H), 3.29 (q, J = 5.5 Hz, 2H), 2.89 (d of t, J = 17 and 7 Hz, 2H), 2.75 (t, J = 5.5 Hz, 2H), 1.95 (d of t, J = 18 and 7 Hz, 2H), 1.82 (br s, NH), 1.31 (t, J = 7 Hz, 6H).

Elemental analysis for C ₁₆ H ₂₇ N ₂ O ₅ P • 4/5 H ₂ O			
Calc'd:	C, 51.55;	H, 7.73;	N, 7.51
Found:	C, 51.69;	H, 7.83;	N, 7.53

To a flask containing 10 % palladium on carbon (3.79 g) under nitrogen was added [2-[(2-(diethoxyphosphinyl)ethyl)amino]ethyl]carbamic acid phenylmethyl ester (3.79 g, 10 mmol) in ethanol (50 mL), followed by 1,4-cyclohexadiene (10.4 mL, 110 mmol). After stirring the suspension overnight, it was filtered through Celite®, preadsorbed onto silica gel, and purified by flash chromatography (7 cm diameter, elution with dried (MgSO₄) 5/ 10/ 85 ammonium hydroxide/ methanol/dichloromethane) to afford [2-[(2-aminoethyl)-amino]ethyl]phosphonic acid diethyl ester as a yellow oil (1.98 g, 88 %); MS (+FAB): 225 (MH⁺, 9), 194 (100), 166 (34), 138 (71), 120 (38), 57 (39), 44 (32); ¹H NMR (CDCl₃, 400 MHz): δ 4.18 - 4.04 (m, 4H), 2.91 (d of t, J = 15 and 7 Hz, 2H), 2.80 (t, J = 5.5 Hz, 2H), 2.68 (t, J = 5.5 Hz, 2H), 1.98 (d of t, J = 18 and 7 Hz, 2H), 1.68 (br s, 3 NH), 1.33 (t, J = 7 Hz, 6H).

Solutions (10 mL each) of 3,4-diethoxy-3-cyclobutene-1,2-dione (1.27 mL, 8.6 mmol) and [2-[(2-aminoethyl)amino]ethyl]phosphonic acid diethyl ester (1.92 g, 8.6 mmol) in ethanol were injected separately via syringe pump into refluxing ethanol (22 mL) over 3 hours. After refluxing overnight, the red-brown solution was preadsorbed onto silica gel and purified by flash chromatography (7 cm diameter, gradient elution with 2.5 - 10 % methanol in ethyl acetate) and recrystallization (methanol in ethyl acetate) to yield [2-(7,8-dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-yl)ethyl]phosphonic acid diethyl ester as a beige solid (0.78 g, 30 %, mp 115-116 °C); IR (KBr, cm⁻¹): 3170, 1780, 1660; MS (+FAB): 303 (MH⁺, 100), 109 (38);

¹H NMR (CDCl₃, 400 MHz): δ 7.64 (br s, NH), 4.16 - 4.06 (m, 4H), 3.80 - 3.73 (m, 2H), 3.63 - 3.60 (m, 2H), 3.48 (t, J = 5 Hz, 2H), 2.31 (d of t, J = 18 and 7.5 Hz, 2H), 1.33 (t, J = 7 Hz, 6H).

Elemental analysis for C ₁₂ H ₁₉ N ₂ O ₅ P			
Calc'd:	C, 47.68;	H, 6.34;	N, 9.27
Found:	C, 47.39;	H, 6.32;	N, 9.22

A solution of [2-(7,8-dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-yl)ethyl]phosphonic acid diethyl ester (0.78 g, 2.6 mmol) and bromotrimethylsilane (2.1 mL, 16 mmol) in dry 1,2-dichloroethane (30 mL) was refluxed under nitrogen for 20 minutes. The cooled reaction mixture was concentrated *in vacuo*, and the residue was dissolved in water (100 mL) and washed with diethyl ether (3 x 50 mL). After concentrating the aqueous layer, the residue was recrystallized from water (25 mL) and methanol (300 mL) to yield a solid beige impurity which was removed by filtration. The filtrate was concentrated and recrystallized from water in isopropanol to yield the title compound as a yellow solid (0.37 g, 58 %, mp 220-270 °C dec); IR (KBr, cm⁻¹): 1800; MS (-FAB): 245 (M-H); ¹H NMR (DMSO/drop of DCl, 400 MHz): δ 3.58 - 3.51 (m, 2H), 3.40 - 3.33 (m, 4H), 2.07 - 1.98 (m, 2H).

Elemental analysis for C ₈ H ₁₁ N ₂ O ₅ P			
Calc'd:	C, 39.04;	H, 4.50;	N, 11.38
Found:	C, 38.60;	H, 4.30;	N, 11.11

Example 8

[2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid

A solution of (3-aminopropyl)carbamic acid phenylmethyl ester (6.11 g, 29 mmol), (2-oxoethyl)-phosphonic acid diethyl ester (5.24 g, 29 mmol) and sodium cyanoborohydride (2.73 g, 43 mmol) in dry methanol (100 mL) was prepared under nitrogen. Methanolic hydrogen chloride was added until the solution remained slightly acidic (pH 6.5). After several hours the reaction was made acidic (pH 1.5) with concentrated hydrochloric acid, the methanol was removed *in vacuo* and the residue was diluted with water (25 mL). After washing with diethyl ether (3 x 30 mL), the aqueous layer was basified to pH 10 with 1 N sodium hydroxide solution, saturated with solid sodium chloride, and then extracted with chloroform (3 x 50 mL). The dried (Na₂SO₄) organic layer was preadsorbed onto silica gel and purified by flash chromatography (7 cm diameter, gradient elution with 5 - 20 % methanol in dichloromethane) to yield [3-[[2-(diethoxyphosphinyl)ethyl]amino]propyl]carbamic acid phenylmethyl ester as a waxy solid (3.86 g, 36 %); IR (neat, cm⁻¹): 3300, 1720, 1250, 1030; MS (+FAB): 373 (MH⁺, 100), 91 (90); ¹H NMR (CDCl₃, 400 MHz): δ 7.36 - 7.29 (m, 5H), 5.58 (br s, NH), 5.09 (s, 2H), 4.15 - 4.04 (m, 4H), 3.29 (q, J = 6 Hz, 2H), 2.91 (d of t, J = 16 and 7 Hz, 2H), 2.71 (t, J = 6 Hz, 2H), 1.98 (d of t, J = 18 and 7 Hz, 2H), 1.70 (p, J = 6 Hz, 2H), 1.31 (t, J = 7 Hz, 6H).

A solution of [3-[[2-(diethoxyphosphinyl)ethyl]amino]propyl]carbamic acid phenylmethyl ester (3.17 g, 8.5 mmol) in absolute ethanol (40 mL) was added over 45 minutes to 3,4-diethoxy-3-cyclobutene-1,2-dione (2.3 mL, 16 mmol) dissolved ethanol (55 mL). After leaving overnight, the reaction mixture was preadsorbed onto silica gel and purified by flash chromatography (7 cm diameter, gradient elution was 2.5-10% methanol in dichloromethane) to yield [3-[[2-(diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid phenylmethyl ester as a viscous oil (3.75 g, 89%); ¹H NMR (CDCl₃, 400 MHz): δ 7.35 (m, 5H), 5.45 (br m, NH), 5.09 (s, 2H), 4.80-4.71 (m, 2H), 4.16-4.09 (m, 4H), 3.90-3.48 (m, 4H), 3.23-3.20 (m, 2H), 2.16-2.05 (m, 2H), 1.85-1.79 (m, 2H), 1.47, 1.41 (t, J=7Hz, 3H), 1.34 (t, J=7 Hz, 6H).

To a flask containing 10% palladium on carbon (2.11 g) under nitrogen was added [3-[[2-(diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid phenylmethyl ester (2.11 g, 4.2 mmol) in absolute ethanol (180 mL), followed by 1,4-cyclohexadiene (4.3 mL, 45 mmol). After stirring for 5 hours, the reaction mixture was filtered through Celite® and concentrated *in vacuo* to yield a crude solid, which was recrystallized from methanol and ethyl acetate (total volume = 20 mL), filtered, and washed with hexane to afford [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid diethyl ester hemihydrate as a cream colored solid (0.82 g, 62%, mp 148-149 °C); IR (KBr, cm⁻¹): 1810; ¹H

NMR (CDCl₃, 400 MHz): δ 7.50 (br s, NH), 4.18-4.10 (m, 4H), 4.09-4.00 (m, 2H), 3.51-3.46 (m, 4H), 2.19 (d of t, J = 18 and 7.5 Hz, 2H), 2.10-2.04 (m, 2H), 1.34 (t, J = 7 Hz, 6H).

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Elemental analysis for C ₁₃ H ₂₁ N ₂ O ₅ P • 1/2 H ₂ O			
Calc'd:	C, 47.99;	H, 6.82;	N, 8.61
Found:	C, 48.23;	H, 6.57;	N, 8.52

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A solution of [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid diethyl ester (1.41 g, 4.5 mmol) and bromotrimethylsilane (4.2 mL, 32 mmol) in dry 1,2-dichloroethane (50 mL) was refluxed for 20 minutes under nitrogen. The cooled reaction mixture was concentrated *in vacuo*, and the residue was dissolved in water (100 mL) and washed with diethyl ether (3 x 75 mL). The water was removed *in vacuo*, and the resulting solid was recrystallized from water and isopropanol to afford [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid one fifth hydrate as a yellow solid (0.91 g, 78%, mp 260-278 °C dec); IR (KBr, cm⁻¹): 1800; ¹H NMR (DMSO 1 drop of DCl, 400 MHz): δ 3.85-3.79 (m, 2H), 3.35-3.32 (m, 2H), 3.25-3.23 (m, 2H), 1.97-1.87 (m, 4H).

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Elemental analysis for C ₉ H ₁₃ N ₂ O ₅ P • 1/5 H ₂ O			
Calc'd:	C, 40.98;	H, 5.12;	N, 10.68
Found:	C, 40.98;	H, 4.98;	N, 10.38

25 Example 9

[2-(4-Hydroxy-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid

A solution of 1,3-diamino-2-hydroxypropane (27.0 g, 0.300 mol) in dry acetonitrile (270 mL) was maintained at ambient temperature with a water bath and was treated with di-*t*-butyl dicarbonate (23.0 mL, 0.100 mol) in acetonitrile (90 mL) over 2 hours with vigorous mechanical stirring and then was left overnight. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in brine (250 mL) to which bromocresol green was added. The mixture was treated with 1 N hydrochloric acid solution until it just turned yellow, washed with dichloromethane (3 x 250 mL), and then made basic (pH 12) by the addition of 2.5 N sodium hydroxide solution. The product was extracted into chloroform (15 x 250 mL), dried with sodium sulfate, and concentrated to yield (3-amino-2-hydroxypropyl)carbamic acid 1,1-dimethylethyl ester as a white solid (7.76g, 41 %, mp 77 - 79 °C); IR (KBr, cm⁻¹): 3360, 1680; MS (+FAB): 191 (MH⁺, 42), 135 (100), 58 (78); ¹H NMR (CDCl₃, 400 MHz): δ 5.04 (br s, NH), 3.65 - 3.60 (m, 1H), 3.34 - 3.22 (m, 1H), 3.12 - 3.05 (m, 1H), 2.83 (d of d, J = 13 and 4 Hz, 1H), 2.63 (d of d, J = 13 and 7.5 Hz, 1H), 1.44 (s, 9H).

A solution of (3-amino-2-hydroxypropyl)carbamic acid 1,1-dimethylethyl ester (7.73 g, 41 mmol), sodium carbonate (6.52 g, 62 mmol) and diethyl 2-bromoethylphosphonate (11.8 mL, 65 mmol) in absolute ethanol (150 mL) was prepared under nitrogen. This mixture was refluxed overnight and was then concentrated *in vacuo*. The residue was dissolved in chloroform (150 mL) and then preadsorbed onto silica gel and purified by flash chromatography (7 cm diameter, gradient elution with 2.5 - 20 % methanol in dichloromethane) to yield [3-[[2-(diethoxyphosphinyl)ethyl]amino]-2-hydroxypropyl]carbamic acid 1,1-dimethylethyl ester as a colorless oil (11.16 g, 77 %); IR (neat, cm⁻¹): 3320, 1710, 1250, 1170, 1040; MS (+FAB): 355 (MH⁺, 68), 255 (90), 58 (100); ¹H NMR (CDCl₃, 400 MHz): δ 5.23 (br s, NH), 4.16 - 4.05 (m, 4H), 3.77 (m, 1H), 3.32 - 2.90 (m, 4H), 2.73 (d of d, J = 12 and 3.5 Hz, 1H), 2.58 (d of d, J = 12 and 8.5 Hz, 1H), 2.00 (d of t, J = 18 and 7 Hz, 2H), 1.43 (s, 9H), 1.32 (t, J = 7 Hz, 6H).

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.0 mL, 34 mmol) in absolute ethanol (180 mL) prepared under nitrogen, was added a solution of [3-[[2-(diethoxyphosphinyl)ethyl]amino]-2-hydroxypropyl]carbamic acid 1,1-dimethylethyl ester (12.11 g, 34 mmol) in ethanol (80 mL) over 1 hour. The reaction mixture was stirred at room temperature overnight and then concentrated *in vacuo*. The residue was dissolved in chloroform (150 mL), preadsorbed onto silica gel, and purified by flash chromatography (7 cm diameter, gradient elution with 2.5 - 15 % methanol in dichloromethane) to yield [3-[[2-(diethoxyphosphinyl)ethyl]amino]-2-hydroxypropyl]carbamic acid 1,1-dimethylethyl ester as a clear viscous oil (11.34 g, 70 %); IR (neat, cm⁻¹): 3350, 1800, 1700; ¹H NMR (CDCl₃, 400 MHz): δ 5.37, 5.19 (br s, NH), 4.82 - 4.72 (m, 3H), 4.16 - 3.11 (m, 11 H), 2.24 - 2.14 (m, 2H), 1.47 - 1.43 (m, 12 H),

1.32 (t, J = 7 Hz, 6H).

A solution of [3-[[2-(diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-hydroxypropyl]carbamic acid 1,1-dimethylethyl ester (11.34 g, 24 mmol) in 96 % formic acid (100 mL) was prepared under nitrogen and stirred at room temperature overnight. The reaction mixture was then concentrated in vacuo to yield a thick yellow oil, which was dissolved in absolute ethanol (120 mL) and added dropwise over 1.5 hours to a solution of diisopropylethylamine (16.7 mL, 96 mmol) in absolute ethanol (360 mL). After refluxing overnight the reaction mixture was concentrated in vacuo and the residue was dissolved in chloroform (150 mL), preadsorbed onto silica gel and purified by flash chromatography (9 cm diameter, gradient elution with 5 - 20 % methanol in dichloromethane) to yield [2-(4-hydroxy-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid diethyl ester as a white solid (5.94 g, 74%, mp 169 - 171 °C); IR (KBr, cm⁻¹): 3330, 3200, 1800, 1250, 1030; MS (+FAB): 333 (MH⁺, 100), 185 (50), 179 (78); ¹H NMR (CDCl₃, 400 MHz): δ 7.18 (br s, NH), 4.52 - 4.44 (m, 1H), 4.20 (m, 1H), 4.14 - 4.04 (m, 4H), 3.79 - 3.70 (m, 2H), 3.57 - 3.54 (m, 2H), 3.36 (d, J = 14 Hz, 1H), 2.33 - 2.13 (m, 2H), 1.32 (d of t, J = 13 and 7 Hz, 6H).

Elemental analysis for C ₁₃ H ₂₁ N ₂ O ₆ P			
Calc'd:	C, 46.89;	H, 6.37;	N, 8.43
Found:	C, 47.07;	H, 6.11;	N, 8.37

To a solution of [2-(4-hydroxy-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid diethyl ester (2.5 g, 7.5 mmol) in dry 1,2-dichloroethane (100 mL) under nitrogen, was added bromotrimethylsilane (9.2 mL, 60 mmol). The reaction mixture was refluxed for 20 min and then concentrated in vacuo to yield a yellow-orange foam, which was dissolved in water (100 mL). The water was washed with ether (3 x 100 mL) and then concentrated in vacuo to yield a solid which was recrystallized from water in isopropanol to yield [2-(4-hydroxy-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid one sixth hydrate as a pale yellow solid (1.79 g, 86 %, mp 268 - 270 °C dec); IR (KBr, cm⁻¹): 3480, 3220, 1820; MS (-FAB): 275 (M-H, 22), 148(100); ¹H NMR (DMSO 1 drop of DCl, 400 MHz): δ 3.90 (m, 1H), 3.85 - 3.74 (m, 2H), 3.46 (d, J = 13 Hz, 1H), 3.34 (d of d, J = 13 and 7 Hz, 1H), 3.28 (m, 2H), 1.98 - 1.89 (m, 2H).

Elemental analysis for C ₉ H ₁₃ N ₂ O ₆ P • 1/6 H ₂ O			
Calc'd:	C, 38.72;	H, 4.81;	N, 10.03
Found:	C, 38.46;	H, 4.59;	N, 10.03

a) Following the procedure of Example 9, with the exception that 2,2-dimethyl-1,3-propanediamine was employed as the reactant, gives [2-(4,4-dimethyl-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid mono hydrate, mp 265 - 282 °C (dec).

Elemental analysis for C ₁₁ H ₁₇ N ₂ O ₅ P • H ₂ O			
Calc'd:	C, 43.14;	H, 6.25;	N, 9.15
Found:	C, 42.98;	H, 6.04;	N, 9.02

b) Following the procedure of Example 9, with the exception that 1,3-propanediamine and diethyl 3-bromopropylphosphonate are the reactants, gives [3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)propyl]phosphonic acid, mp 244 - 248 °C.

Elemental analysis for C ₁₀ H ₁₅ N ₂ O ₅ P			
Calc'd:	C, 43.80;	H, 5.51;	N, 10.23
Found:	C, 43.93;	H, 5.42;	N, 10.18

c) Following the procedure of Example 9, with the exception that 1,3-propanediamine and diethyl (E)-(3-chloro-1-propenyl)phosphonate are the reactants, gives [(E)-3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-

en-2-yl)-1-propenyl]phosphonic acid one sixth hydrate, mp 255 - 275 °C (dec).

Elemental analysis for $C_{10}H_{13}N_2O_5P \cdot 1/6 H_2O$			
Calc'd:	C, 43.64;	H, 4.88;	N, 10.18
Found:	C, 43.69;	H, 4.68;	N, 10.02

Example 10

8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-ene-2-acetic acid

A solution of (3-aminopropyl)carbamic acid phenylmethyl ester (7.08 g, 34 mmol) and N,N-diisopropylethylamine (4.5 mL, 26 mmol) in anhydrous dimethylformamide (100 mL) under nitrogen was cooled to 10 °C and treated with t-butyl bromoacetate (2.80 mL, 17 mmol) over 5 minutes. After one hour the bath was removed and the reaction mixture was stirred overnight, poured into water (500 mL), and made basic (pH 12) with 2.5 N sodium hydroxide solution. The aqueous layer was extracted with dichloromethane (2 x 250 mL), which was dried over sodium sulfate and concentrated in vacuo with heat to remove dimethylformamide. The residue was purified by flash chromatography (9 cm diameter, gradient elution with 2.5 - 3.5 % methanol in dichloromethane) to yield [3-[[[(1,1-dimethylethoxy)carbonyl]methyl]amino]propyl]carbamic acid phenylmethyl ester as a pale yellow oil (4.50 g, 82 %); 1H NMR ($CDCl_3$, 200 MHz): δ 7.35 (m, 5H), 5.43 (br s, NH), 5.09 (s, 2H), 3.35 - 3.24 (m, 4H), 2.68 (t, J = 6.5 Hz, 2H), 1.68 (p, J = 6.5 Hz, 2H), 1.46 (s, 9H).

An ethanolic solution (60 mL) of [3-[[[(1,1-dimethylethoxy)carbonyl]methyl]amino]propyl]carbamic acid phenylmethyl ester (4.49 g, 13.9 mmol) under nitrogen was added to 3,4-diehoxy-3-cyclobutene-1,2-dione (2.0 mL, 13 mmol) in the same solvent (60 mL) over 1 hour. After 3.5 more hours, the reaction mixture was preadsorbed onto silica gel and purified by flash chromatography (7.5 cm diameter, gradient elution with 30 to 60 % ethyl acetate in petroleum ether) to afford [3-[[[(1,1-dimethylethoxy)carbonyl]methyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid phenylmethyl ester as a viscous colorless oil (5.26 g, 91 %); MS (+Cl): 447 (MH^+ , 100), 391 (38); 1H NMR ($CDCl_3$, 400 MHz): δ 7.35 (m, 5H), 5.55, 4.97 (br m, NH), 5.10 (s, 2H), 4.75, 4.73 (q, J = 7 Hz, 2H), 4.29, 3.99 (s, 2H), 3.74, 3.49 (t, J = 6.5 Hz, 2H), 3.29 - 3.22 (m, 2H), 1.84 - 1.75 (m, 2H), 1.48, 1.47 (s, 9H), 1.45 - 1.40 (m, 3H).

To a cooled (20 °C) flask containing 10 % palladium on carbon (5.25 g) under nitrogen was added [3-[[[(1,1-dimethylethoxy)carbonyl]methyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid phenylmethyl ester (5.25 g, 11.8 mmol) in ethanol (500 mL), followed by 1,4-cyclohexadiene (11 mL, 0.12 mol) over 5 min. After 5 hours, the suspension was filtered through Celite® with generous ethanol washing (1 L). The ethanol was evaporated and the residue was dissolved in dichloromethane and purified by flash chromatography (7.5 cm diameter, gradient elution with 2.5 - 3 % methanol in dichloromethane) to yield (8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)acetic acid 1,1-methylethyl ester as a white solid (2.59 g, 82 %, mp 167 - 168 °C); IR (KBr, cm^{-1}): 3200, 1800, 1720; MS (EI): 266 (M^+ , 42), 210 (33), 166 (37), 165 (100), 154 (58), 138 (37), 70 (58); 1H NMR (DMSO, 400 MHz): δ 8.62 (br s, NH), 4.38 (s, 2H), 3.36 - 3.27 (m, 4H), 1.91 (m, 2H), 1.40 (s, 9H).

Elemental analysis for $C_{13}H_{18}N_2O_4$			
Calc'd:	C, 58.63;	H, 6.81;	N, 10.52
Found:	C, 58.57;	H, 6.78;	N, 10.40

An ethanolic (86 mL) solution of (8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)acetic acid 1,1-dimethylethyl ester (2.29 g, 8.60 mmol) was treated at room temperature with 2.5 N sodium hydroxide solution (3.5 mL, 8.7 mmol) and left stirring overnight. The suspension was filtered, washing with ethyl acetate to give a solid which was recrystallized from methanol / water / isopropanol (final volume 50 mL) to afford (8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)acetic acid sodium salt hydrate (1.43 g, 66 %, mp 280 - 300 °C dec); MS (-FAB): 231 (M-H, 37), 209 (M-Na, 100); 1H NMR (DMSO 1 drop of DCl, 400 MHz): δ 4.40 (s, 2H), 3.36 - 3.25 (m, 4H), 1.89 (m, 2H).

Elemental analysis for $C_9H_9N_2NaO_4 \cdot H_2O$			
Calc'd:	C, 43.21;	H, 4.43;	N, 11.20
Found:	C, 43.29;	H, 4.38;	N, 11.32

a) Following the procedure of Example 10, with the exception that ethyl 3-bromopropionate was employed as a reactant, gives 3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)propanoic acid sodium salt sesquihydrate, mp 310 (dec).

Elemental analysis for $C_{10}H_{11}N_2NaO_4 \cdot 1.5 H_2O$			
Calc'd:	C, 44.04;	H, 4.99;	N, 10.27
Found:	C, 44.28;	H, 5.15;	N, 10.24

Example 11

2-[(1H-Tetrazol-5-yl)methyl]-2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione

A solution of (3-aminopropyl)carbamic acid 1,1-dimethylethyl ester (6.00 g, 34 mmol), prepared by the method of Saari et al., *J. Med. Chem.*, **33**, 97 (1990), in absolute ethanol (90 mL) was treated with sodium carbonate (3.96 g, 37 mmol) followed by a solution of bromoacetonitrile (2.6 mL, 37 mmol) in ethanol (30 mL) over 45 min. After stirring at room temperature overnight, the contents of the flask were filtered, preadsorbed onto silica gel, and purified by flash chromatography (7 cm diameter, elution with 2.5 % methanol in dichloromethane) to afford [3-(cyanomethylamino)propyl]carbamic acid 1,1-dimethylethyl ester as a yellow oil (3.99 g, 55 %); IR (neat, cm^{-1}): 3330, 2240, 1700; MS (+CI): 214 (MH^+ , 20), 187 (76), 158 (100), 131 (44); 1H NMR ($CDCl_3$, 400 MHz): δ 4.80 (br s, NH), 3.61 (s, 2H), 3.22 (q, J = 6.5 Hz, 2H), 2.79 (t, J = 6.5 Hz, 2H), 1.69 (p, J = 6.5 Hz, 2H), 1.45 (s, 9H).

A solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (2.6 mL, 18 mmol) in absolute ethanol (90 mL) was treated with [3-(cyanomethylamino)propyl]carbamic acid 1,1-dimethylethyl ester (3.90 g, 18 mmol) in ethanol (30 mL) over 90 min. After 40 hours the reaction mixture was evaporated, dissolved in dichloromethane, preadsorbed onto silica gel, and purified by flash chromatography (7 cm diameter, gradient elution with 0 - 5 % methanol in dichloromethane) to yield [3-[(cyanomethyl)-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid 1,1-dimethylethyl ester as a yellow oil (5.48 g, 90%); IR (neat, cm^{-1}): 3360, 1800; MS (+FAB): 282 (76), 238 (98), 158 (100); 1H NMR ($CDCl_3$, 400 MHz): δ 4.81 (q, J = 7 Hz, 2H), 4.75 (br s, NH), 4.45, 3.66 (s, 2H), 3.84, 3.60 (br m, 2H), 3.26 - 3.15 (m, 2H), 1.91 (p, J = 6.5 Hz, 2H), 1.50 (t, J = 7 Hz, 3H), 1.45 (s, 9H).

A solution of [3-[(cyanomethyl)-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid 1,1-dimethylethyl ester (5.48 g, 16 mmol) in 96 % formic acid (40 mL) under nitrogen was prepared. After 24 hours the solvent was removed and the residue was dissolved in isopropanol and concentrated several times. Ethanol (40 mL) was added and the suspension was stirred overnight and filtered to afford (8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)acetonitrile one eighth hydrate as a white solid (1.50 g, 48 %, mp 215 - 218 °C); IR (KBr, cm^{-1}): 3220, 1810; MS (DEI): 191 (M^+ , 57), 135 (41), 70 (41), 43 (70), 41 (100); 1H NMR (DMSO, 400 MHz): δ 8.83 (br s, NH), 4.84 (s, 2H), 3.40 - 3.30 (m, 4H), 1.95 (m, 2H).

Elemental analysis for $C_9H_9N_3O_2 \cdot 1/8 H_2O$			
Calc'd:	C, 55.93;	H, 4.69;	N, 21.74
Found:	C, 55.99;	H, 4.76;	N, 21.90

To a solution of (8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)acetonitrile one eighth hydrate (1.54 g, 8.0 mmol) in dry dimethylformamide (35 mL) under nitrogen, was added sodium azide (0.79 g, 12 mmol) and ammonium chloride (0.65 g, 12 mmol). The reaction mixture was slowly heated to 125 °C, maintained at this temperature for 2 hours, cooled to room temperature, and then filtered. The concentrated filtrate was dissolved in water and evaporated. The residue was recrystallized from methanol to yield 2-[(1H-tetrazol-5-yl)methyl]-2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione one third hydrate as off-white crystals (1.18 g, 61 %, mp 264 - 267 °C); IR (KBr, cm^{-1}): 3200, 1810; 1H NMR (DMSO, 400 MHz): δ 8.70 (s, NH), 5.24 (s, 2H),

3.34 - 3.28 (m, 4H), 1.92 (m, 2H).

Elemental analysis for $C_9H_{10}N_6O_2 \cdot 1/3 H_2O$			
Calc'd:	C, 45.00;	H, 4.48;	N, 34.98
Found:	C, 45.28;	H, 4.21;	N, 34.76

a) Following the procedure of Example 11, with the exception that 3-bromopropionitrile was employed as a reactant, gives 2-[2-(1H-tetrazol-5-yl)ethyl]-2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione, mp 255 - 262 (dec).

Elemental analysis for $C_{10}H_{12}N_6O_2$			
Calc'd:	C, 48.38;	H, 4.87;	N, 33.85
Found:	C, 48.10;	H, 4.80;	N, 34.19

Example 12

[2-(9,10-Dioxo-2,7-diazabicyclo[6.2.0]dec-1(8)-en-2-yl)ethyl]phosphonic acid

A solution of 1,4-diaminobutane (30 mL, 0.30 mol) in dry tetrahydrofuran (90 mL) was maintained at 0 °C and was treated with di-*t*-butyl dicarbonate (23 mL, 0.10 mol) in tetrahydrofuran (90 mL) over 1.5 hours with vigorous mechanical stirring and then was left overnight. The reaction mixture was concentrated in vacuo and the residue was dissolved in water (100 mL) to which bromocresol green was added. The mixture was treated with 1 N hydrochloric acid solution until it just turned yellow, washed with dichloromethane (2 x 250 mL), and then made basic (pH 12) by the addition of 2.5 N sodium hydroxide solution. The product was extracted into chloroform (6 x 250 mL), dried with sodium sulfate, and concentrated to yield (4-aminobutyl)carbamic acid 1,1-dimethylethyl ester as a yellow oil (13.4 g, 71 %); IR (neat, cm^{-1}): 3350, 1700; MS (EI): 188 (M^+ , 4), 132 (56), 115 (33), 70 (100); 1H NMR ($CDCl_3$, 400 MHz): δ 4.76 (br s, NH), 3.11 (q, J = 6 Hz, 2H), 2.70 (t, J = 6 Hz, 2H), 1.58 - 1.45 (m, 4H), 1.43 (s, 9H).

A solution of (4-aminobutyl)carbamic acid 1,1-dimethylethyl ester (13.3 g, 71 mmol), sodium carbonate (11.25 g, 106 mmol) and diethyl 2-bromo-ethylphosphonate (20 mL, 104 mmol) in absolute ethanol (150 mL) was prepared under nitrogen. This mixture was refluxed overnight and was then concentrated in vacuo. The residue was dissolved in chloroform (150 mL) and then preadsorbed onto silica gel and purified by flash chromatography (7 cm diameter, gradient elution with 5 - 30 % methanol in dichloromethane) to yield [4[[2-(diethoxyphosphinyl)ethyl]amino]butyl]carbamic acid 1,1-dimethylethyl ester as a colorless oil (13.7 g, 55 %); MS (+FAB): 353 (MH^+ , 100), 150 (68), 56 (83); 1H NMR ($CDCl_3$, 400 MHz): δ 5.01 (br s, NH), 4.17 - 4.03 (m, 4H), 3.15 - 3.08 (m, 2H), 2.92 (d of t, J = 15 and 7.5 Hz, 2H), 2.84 (br s, NH), 2.66 (br t, J = 7 Hz, 2H), 2.02 (d of t, J = 18 and 7.5 Hz, 2H), 1.56 - 1.52 (m, 4H), 1.43 (s, 9H), 1.33 (t, J = 7 Hz, 6H).

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (5.8 mL, 39 mmol) in absolute ethanol (200 mL) prepared under nitrogen, was added a solution of [4[[2-(diethoxyphosphinyl)ethyl]amino]butyl]carbamic acid 1,1-dimethylethyl ester (13.7 g, 39 mmol) in ethanol (75 mL) over 1.75 hour. The reaction mixture was stirred at room temperature overnight and then concentrated in vacuo. The residue was dissolved in chloroform (150 mL), preadsorbed onto silica gel, and purified by flash chromatography (9 cm diameter, elution with 2.5 % methanol in dichloromethane) to yield [4-[[2-(diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]carbamic acid 1,1-dimethylethyl ester as a yellow viscous oil (16.8 g, 90 %).

A solution of [4-[[2-(diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]carbamic acid 1,1-dimethylethyl ester (16.8 g, 35 mmol) in 96 % formic acid (100 mL) was prepared under nitrogen and stirred at room temperature overnight. The reaction mixture was then concentrated in vacuo to yield a thick yellow oil, which was dissolved in absolute ethanol (125 mL) and added dropwise over 1.5 hours to a solution of diisopropylethylamine (17 mL, 98 mmol) in absolute ethanol (375 mL). After refluxing overnight the reaction mixture was concentrated in vacuo and the residue was dissolved in chloroform (150 mL), preadsorbed onto silica gel, and purified by flash chromatography (9 cm diameter, gradient elution with 5 - 10 % methanol in dichloromethane) to yield [2-(9,10-Dioxo-2,7-diazabicyclo[6.2.0]dec-1(8)-en-2-yl)ethyl]phosphonic acid diethyl ester as a pale yellow solid (9.65 g, 83 %, mp 103 - 105 °C); IR (KBr, cm^{-1}):

3440, 3230, 1795; MS (+FAB): 331 (MH⁺, 100), 109 (31); ¹H NMR (CDCl₃, 400 MHz): δ 7.14 (br s, NH), 4.16 - 4.05 (m, 6H), 3.39 - 3.36 (m, 4H), 2.17 (d of t, J = 19 and 7.5 Hz, 2H), 1.74 - 1.68 (m, 4H), 1.33 (t, J = 7 Hz, 6H).

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Elemental analysis for C ₁₄ H ₂₃ N ₂ O ₅ P			
Calc'd:	C, 50.91;	H, 7.02;	N, 8.48
Found:	C, 50.76;	H, 6.82;	N, 8.37

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To a solution of [2-(9,10-Dioxo-2,7-diazabicyclo[6.2.0]dec-1(8)-en-2-yl)ethyl]phosphonic acid diethyl ester (7.60 g, 23 mmol) in dry 1,2-dichloroethane (300 mL) under nitrogen, was added bromotrimethylsilane (25 g, 160 mmol). The reaction mixture was refluxed for 25 min and then concentrated in vacuo to yield a dark rust oil, which was dissolved in water (250 mL). The water was washed with ether (3 x 250 mL) and then concentrated in vacuo to yield a yellow orange solid which was recrystallized from water (100 mL) to yield [2-(9,10-Dioxo-2,7-diazabicyclo[6.2.0]dec-1(8)-en-2-yl)ethyl]phosphonic acid hydrate as a tan solid (3.80 g, 60 %, mp 266 - 271 °C dec); IR (KBr, cm⁻¹): 3350, 3260, 1800; MS (-FAB): 273 (M-H); ¹H NMR (DMSO, 400 MHz): δ 8.32 (br s, NH), 3.94 - 3.87 (m, 2H), 3.31 - 3.28 (m, 2H), 3.22 - 3.18 (m, 2H), 1.96 - 1.87 (m, 2H), 1.61 - 1.49 (m, 4H).

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Elemental analysis for C ₁₀ H ₁₅ N ₂ O ₅ P • H ₂ O			
Calc'd:	C, 41.10;	H, 5.86;	N, 9.59
Found:	C, 41.22;	H, 5.76;	N, 9.65

25

In a manner analogous to the procedures of Examples 7 and 8, the following compounds are obtained:

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Example	Compound
13	[(E)-3-(7,8-Dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-yl)-1-propenyl]phosphonic acid
14	[3-(7,8-Dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-yl)propyl]phosphonic acid

It was determined that the compounds of this invention are competitive NMDA antagonists by determining their ability to inhibit binding of 3-(2-carboxypiperazinyl-4-yl)propyl-1-phosphonic acid (CPP), a known competitive NMDA antagonist, at NMDA receptors in rat brain homogenate. In a manner similar to the procedure of Murphy et al., J. Pharmacol. Exp. Therap. 240 (3) 778 (1987), rat brain homogenates from which endogenous glutamate had been removed were incubated with (3H)CPP (8nM), the compound being tested and then buffer each for 15 minutes at 23 °C to obtain a final volume of 2 milliliters. The amount of radio ligand displaced by the test compound is expressed as a percentile of the radio ligand displaced by NMDA. The inhibitory concentration of test compound that will displace 50% of the labeled CPP is determined from dose-response evaluations.

The properties of these compounds were also directly established by demonstrating the NMDA antagonist properties of representative compounds in male Swiss-albino mice (CD-1 strain, Charles River) 18-22 grams in weight after 18 hours of food deprivation which had been habituated to an observation chamber for 30 minutes. The mice were pretreated with the representative test compounds followed thirty minutes later with NMDA (195 mg/kg, i.p., the ED₅₀ dose for generalized myoclonus). The mice were then observed for 30 minutes, noting the latency of onset of generalized myoclonus (uncontrollable hind leg scratching of limbs and/or torso muscle jerking with loss of righting reflex) and death. From the latter, the ED₅₀ for survival is determined. In this standard experimental test procedure, the specific compounds tested and their activity, which representatively establish the activity for all the compounds herein, is presented in the following Table.

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Table

	Compound of Example	CPP Binding IC ₅₀ (μM)	NMDA Induced Lethality ED ₅₀ (mp/kg)
5	1	1.6	>100
	1(a)	190	>100
	1(b)	2.3	>100
	1(c)	10.2	>100
	2	5.2	>100
10	2(a)	19.6	>100
	2(b)	>100	>100
	3	10.5	>100
	3(a)	30	>100
	3(b)	50% (100)	>100
15	4	0.471	28.7
	4(a)	>10	>100
	4(b)	2.59	>100
	4(c)	68% (10)	>30
	5	52% (10)	>30
20	6	1.0	50% (50)
	6(a)	>10	>150
	7	0.092	6.2
	8	0.030	2.1
	9	0.019	1.8
25	9(a)	0.28	50% (5)
	9(b)	>1	>10
	9(c)	>10	>5
	10	0.55	>20
	10(a)	0.34	>20
30	11	0.038	>10
	11(a)	40% (10)	>5
	12	0.041	80% (5)

Where the displacement of CPP binding is expressed as a percentage, it is at the μM concentration given at the concentration in the parenthesis. Similarly, where percent inhibition of lethality at dose in parenthesis.

Thus, the compounds of this invention demonstrate the ability to antagonize NMDA-induced lethality in vivo in mice. They compete with 3-(2-carboxypiperazinyl-4-yl)-propyl-1-phosphonic acid (CPP), a known competitive NMDA-antagonist, for its binding site. The compounds of the present invention are, therefore, competitive NMDA antagonists.

The compounds of the present invention are active against NMDA-induced lethality and are useful in the treatment of CNS disorders such as convulsions, brain cell damage and related neurodegenerative disorders, including senile dementia, Alzheimer's disease, Huntingdon's chorea, stroke, hypoglycemia, cerebral palsy, cerebral ischemia, epilepsy, and olivo-ponto cerebellar atrophy.

Hence, there is herewith provided in addition to the novel compounds, supra, a method for the preparation of a medicament for preventing neurodegenerative disorders induced by overstimulation of NMDA receptors in brain and spinal cord by excitatory amino acids, which comprises administering to a mammal suffering from such degenerative disease states, an anticonvulsant, neuroprotective amount of an NMDA antagonist of this invention.

As such, the compounds of this invention may be administered neat or with a pharmaceutical carrier to a patient in need thereof. The pharmaceutical carrier may be solid or liquid.

Accordingly, this invention also provides a pharmaceutical composition comprising a compound of formula I as shown and defined hereinabove or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

- 5 Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds can also be administered orally either in liquid or solid composition form.

- 20 Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

- 25 To determine the effective amount of compound to be administered in alleviation of CNS degenerative dysfunctions, the physician need only evaluate the effects of a given NMDA antagonist in the patient by incrementally increasing the oral dosage from about 1 mg/kg to about 20 mg/kg until the desired symptomatic relief level is achieved. The continuing dose regimen may then be modified to achieve the desired result, with the range of about 1 to 100 mg/day. Similar techniques are followed by determining the effective dose range upon i.v. or i.m. administration. When using the compounds prophylactically to arrest declining cognitive function as in Alzheimer's dementia, a more subjective approach is taken such as by relating the drug dosage to improved memory responses or analogous desired responses which can be related to relief of overstimulation of the excitatory amino acid receptors.

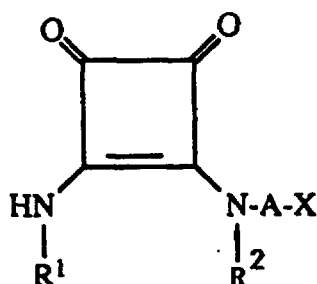
35 Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE

1. A compound of the formula: in which

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(I)

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R¹ is hydrogen, alkyl of 1 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms;

R² is hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms;

or

R¹ and R² taken together are Z where Z is -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- or -CH₂C(R⁸)(R⁹)-C(R¹⁰)-(R¹¹)CH₂-, where R⁶, R⁸ and R¹⁰ are, independently, hydrogen, alkyl of 1 to 6 carbon atoms or



The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds can also be administered orally either in liquid or solid composition form.

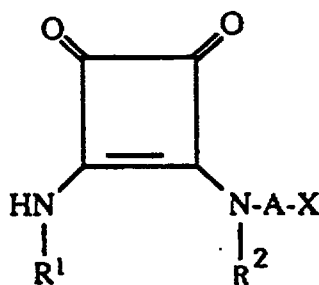
Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

To determine the effective amount of compound to be administered in alleviation of CNS degenerative dysfunctions, the physician need only evaluate the effects of a given NMDA antagonist in the patient by incrementally increasing the oral dosage from about 1 mg/kg to about 20 mg/kg until the desired symptomatic relief level is achieved. The continuing dose regimen may then be modified to achieve the desired result, with the range of about 1 to 100 mg/day. Similar techniques are followed by determining the effective dose range upon i.v. or i.m. administration. When using the compounds prophylactically to arrest declining cognitive function as in Alzheimer's dementia, a more subjective approach is taken such as by relating the drug dosage to improved memory responses or analogous desired responses which can be related to relief of overstimulation of the excitatory amino acid receptors.

Claims

Claims for the following Contracting States : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE

1. A compound of the formula: in which



(I)

R¹ is hydrogen, alkyl of 1 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms;

R² is hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms;

or

R¹ and R² taken together are Z where Z is -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- or -CH₂C(R⁸)(R⁹)-C(R¹⁰)-(R¹¹)CH₂-, where R⁶, R⁸ and R¹⁰ are, independently, hydrogen, alkyl of 1 to 6 carbon atoms or



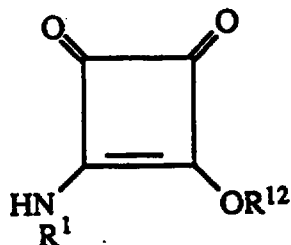
hydroxyl and R⁷, R⁸ and R¹¹ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms,
A is alkylene of 1 to 6 carbon atoms or alkenylene of 2 to 6 carbon atoms;

X is CO₂R³ in which R³ is hydrogen or alkyl of 1 to 6 carbon atoms, P(O)(OR⁴)(OR⁵) in which R⁴ and R⁵ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms, 3,5-dioxo-1,2,4-oxadiazolidin-2-yl or 5-tetrazolyl; or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in Claim 1 in which R¹ and R² are, independently, hydrogen, methyl, allyl, methallyl or benzyl or R¹ and R² taken together are -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- or -CH₂C(R⁸)(R⁹)-C(R¹⁰)(R¹¹)CH₂-, where R⁶, R⁸ and R¹⁰ are independently, hydrogen, alkyl of 1 to 6 carbon atoms or hydroxyl and R⁷, R⁹ and R¹¹ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms.
3. A compound as claimed in Claim 1 or Claim 2 where A is alkylene of 1 to 4 carbon atoms or trans-2-butenylene.
4. A compound as claimed in any one of Claims 1 to 3 wherein X is carboxyl, phosphonyl or 5-tetrazolyl.
5. A compound as claimed in Claim 1 which is one of the following:
 - N-(2-amino-3,4-dioxo-1-cyclobuten-1-yl)beta alanine,
 - N-(2-amino-3,4-dioxo-1-cyclobutenyl)glycine ethyl ester;
 - 2-[2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]-1,2,4-oxadiazolidine-3,5-dione;
 - N-[2-(methylamino)-3,4-dioxo-1-cyclobutenyl]beta-alanine;
 - N-(2-amino-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)glycine;
 - N-(2-amino-3,4-dioxo-1-cyclobutenyl)-N-(2-methyl-2-propenyl)glycine;
 - [[2-(2-amino-3,4-dioxo-1-cyclobutenyl)amino]methyl]phosphonic acid;
 - [3-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]phosphonic acid;
 - [4-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]phosphonic acid;
 - [(E)-4-[(2-amino-3,4-dioxo-1-cyclobutenyl-1-yl)amino]-2-butenyl]phosphonic acid;
 - [[2-(2-amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]methyl]phosphonic acid;
 - [(E)-3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-1-propenyl]-phosphonic acid;
 - 2-[2-(1H-tetrazol-5-yl)ethyl]-2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione;
 - N-(2-amino-3,4-dioxo-1-cyclobutenyl)glycine;
 - 4-[2-amino-3,4-dioxo-1-cyclobutenyl]amino]butanoic acid;
 - 3-[[3,4-dioxo-2-[(phenylmethyl)amino]-1-cyclobutenyl]amino]propanoic acid; or N-(2-amino-3,4-dioxo-1-cyclobutenyl)-N-(phenylmethyl)glycine; or a pharmaceutically acceptable salt thereof.
6. A compound as claimed in Claim 1 which is:
 - [2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid or a pharmaceutically acceptable salt thereof;
 - [2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid, or a pharmaceutically acceptable salt thereof;
 - [2-(7,8-dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-yl)ethyl]phosphonic acid, or a pharmaceutically acceptable salt thereof;
 - [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid or a pharmaceutically acceptable salt thereof;
 - [2-(4-hydroxy-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid, or a pharmaceutically acceptable salt thereof;
 - [2-(4,4-dimethyl-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid, or a pharmaceutically acceptable salt thereof;
 - 2[3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl) propyl]phosphonic acid or a pharmaceutically acceptable salt thereof;
 - 8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-ene-2-acetic acid, or a pharmaceutically acceptable salt thereof;
 - 3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)propanoic acid, or a pharmaceutically acceptable salt thereof;
 - 2-[(1H-tetrazol-5-yl)methyl]-2,6-diazabicyclo [5.2.0]non-1(7)-ene-8,9-dione, or a pharmaceutically acceptable salt thereof; or
 - [2-(9,10-dioxo-2,7-diazabicyclo[6.2.0]dec-1(8)-en-2-yl)ethyl]phosphonic acid, or a pharmaceutically acceptable salt thereof.

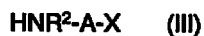


7. A compound as claimed in any one of Claims 1 to 6 when in the form of alkali metal, alkaline earth metal or ammonium salt.
8. A process for preparing a compound of formula I as defined in Claim 1 which comprises
- reacting a compound of formula (II)



(II)

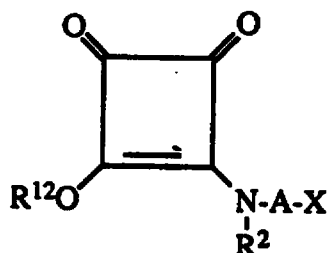
wherein R^1 is as defined in Claim 1 and OR^{12} represents any alkoxy or aralkoxy leaving group, with a compound of formula (III):



wherein R^2 , A and X are as defined in Claim 1 or a salt or protected form thereof, if required removing any protecting group; to give a compound of formula I wherein R^2 is as defined in Claim 1 if desired isolating as a pharmaceutically acceptable salt;

or

- reacting a compound of formula (IV)



(IV)

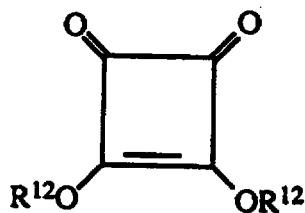
wherein X, R^2 and R^{12} are as defined above or a salt or protected form thereof with a compound of formula



wherein R^1 is as defined in Claim 1 and removing any protecting group to give a corresponding compound of formula I or a salt thereof;

or

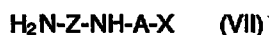
- reacting a compound of formula (VI)



(VI)



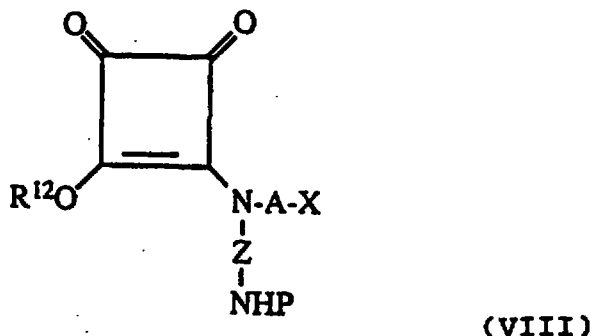
wherein R^{12} is as defined above and each is the same or different, with a compound of formula



wherein X is as defined in Claim 1 or a salt or protected form thereof, Z and A are as defined in Claim 1, if required removing any protecting group; to give a corresponding compound having formula (I) wherein R^1 and R^2 taken together are Z, A and X are as defined above;

or

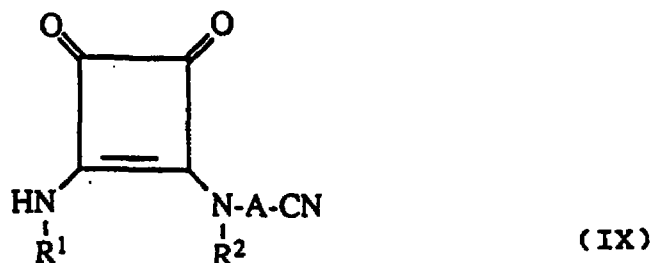
d) deprotecting, selectively if required, and cyclising a compound of formula (VIII)



wherein X, Z, R^{12} and A are as defined above or a salt or protected form thereof, and P is an amino protecting group, which is preferably selectively removable if X is protected, to give a corresponding compound having formula I where R^1 and R^2 are Z if required also removing any protecting group on X;

or

e) reacting a compound of formula (IX)



wherein R^1 , R^2 and A are as defined in Claim 1, with an azide, to give a corresponding compound of formula I where X is 5-tetrazolyl;

or

f) converting a compound of formula I wherein R^3 , R^4 and R^5 are alkyl groups to give a compound of formula I wherein R^3 , R^4 and R^5 are hydrogen or a salt thereof;

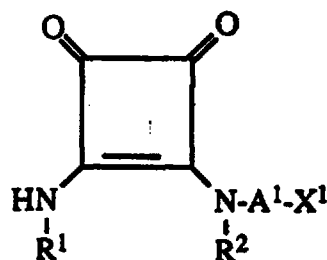
or

g) acidifying a salt of a compound of formula I to give the free acid or basifying an acid of formula I to give a salt thereof;

or



h) thermolysing a compound of formula (X)

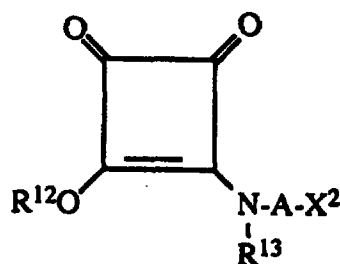


(X)

wherein R^1 is as defined above, X^1 is CO_2R^3 or $-PO(OR^4)(OR^5)$ where R^3 , R^4 and R^5 are all alkyl; 3,5-dioxo-1,2,4-oxadiazolidin-2-yl or protected 5-tetrazolyl, and $-A^1-$ represents alkylene of 2 to 6 carbon atoms substituted by a $S(O)_m$ aryl radical where m represents 1 or 2, if required removing any protecting group to give a corresponding compound of formula I wherein A is alkenylene of 2 to 6 carbon atoms.

9. A pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof as claimed in any one of Claims 1 to 7 and a pharmaceutically acceptable carrier.

10. A compound of general formula (XII):



(XII)

or a salt thereof,

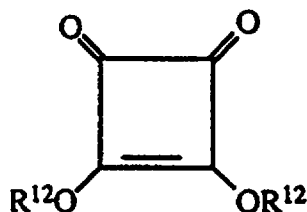
where X^2 represents CN, $COOR^{14}$ where R^{14} is hydrogen, alkyl of 1 to 6 carbon atoms or a carboxyl protecting group, $-PO(OR^{15})(OR^{16})$ where R^{15} and R^{16} are hydrogen or alkyl of 1 to 6 carbon atoms, 3,5-dioxo-1,2,4-oxadiazolidinyl or optionally protected 5-tetrazolyl; R^{12} represents an alkoxy or aralkoxy leaving group and R^{13} represents hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, phenylalkyl of 7 to 12 carbon atoms or NHP wherein P is an amino protecting group and A and Z are as defined in Claim 1.

11. A compound as claimed in Claim 10 wherein R^{13} is hydrogen, methyl, alkyl, methallyl or benzyl.
12. A compound as claimed in Claim 10 wherein P is benzyloxycarbonyl or a substituted derivative thereof.
13. A compound as claimed in anyone of Claims 10 to 12 wherein R^{12} is methyl or ethyl.
14. A compound as claimed in any one of Claims 11 to 13 wherein R^{14} , R^{15} and R^{16} are selected from methyl and ethyl.
15. A compound as claimed in Claim 11 which is one of the following:
 [2-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid, diethyl ester;
 [[2-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]methyl]phosphonic acid, diethyl ester;
 [3-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]phosphonic acid, diethyl ester;
 [4-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]phosphonic acid, diethyl ester;
 [(E)-4-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-butenyl]phosphonic acid diethyl ester;



[2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid diethyl ester;
 [[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)methylamino]methyl]phosphonic acid diethyl ester;
 [3-[[2-(diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid
 phenylmethyl ester;
 [3-[[2-(diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-hydroxypropyl]carbamic
 acid 1,1-dimethylethyl ester;
 [3-[[1,1-Dimethylethoxycarbonyl)methyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic
 acid phenylmethyl ester;
 [3-[(Cyanomethyl)-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid 1,1-dimethylethyl
 ester; or [4-[[2-(Diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]carbamic
 acid 1,1-dimethyl ethyl ester.

16. A process for preparing a compound of formula XII as shown and defined in Claim 11 which comprises
 a) reacting a compound of formula (VI)



(VI)

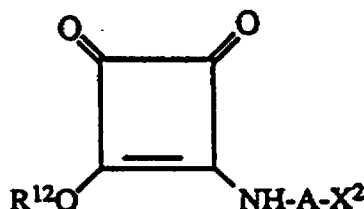
with a compound of formula



where A, R^{12} , R^{13} and X^2 are as defined in Claim 11, to give a corresponding compound of formula XII;

or

b) N-alkylating a compound of formula XIV:



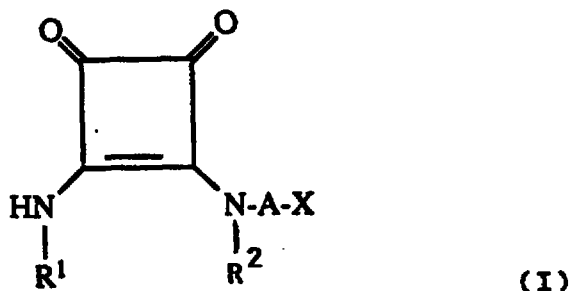
(XIV)

where R^{12} , A and X^2 are as defined above in the presence of a strong base, with a compound of formula $\text{R}^2\text{-halo}$ where halo is a halogen and R^2 is as defined above except hydrogen to give a corresponding compound of formula (XII).



Claims for the following Contracting State : ES

1. A process for preparing a compound of the formula:



in which

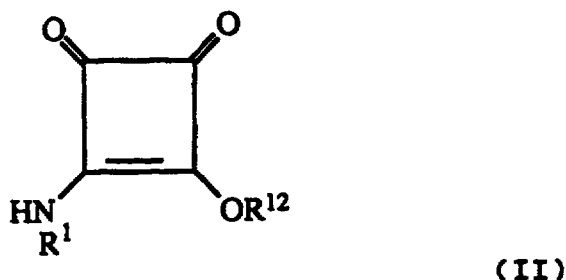
R¹ is hydrogen, alkyl of 1 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms; R² is hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms; or

R¹ and R² taken together are Z where Z is -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- or -CH₂C(R⁸)(R⁹)-C(R¹⁰)-(R¹¹)CH₂-, where R⁶, R⁸ and R¹⁰ are, independently, hydrogen, alkyl of 1 to 6 carbon atoms or hydroxyl and R⁷, R⁹ and R¹¹ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms,

A is alkylene of 1 to 6 carbon atoms or alkenylene of 2 to 6 carbon atoms;

X is CO₂R³ in which R³ is hydrogen or alkyl of 1 to 6 carbon atoms, P(O)(OR⁴)(OR⁵) in which R⁴ and R⁵ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms, 3,5-dioxo-1,2,4-oxadiazolidin-2-yl or 5-tetrazolyl; or a pharmaceutically acceptable salt thereof, which comprises one of the following:

- a) reacting a compound of formula (II)



herein R¹ is as defined in above and OR¹² represents any alkoxy or aralkoxy leaving group, with a compound of formula (III):

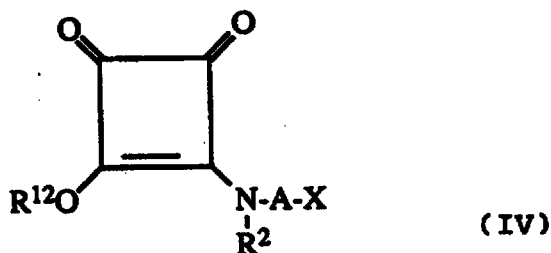


wherein R², A and X are as defined in above or a salt or protected form thereof, if required removing any protecting group; to give a compound of formula I wherein R² is as defined in above if desired isolating as a pharmaceutically acceptable salt;

or



b) reacting a compound of formula (IV)



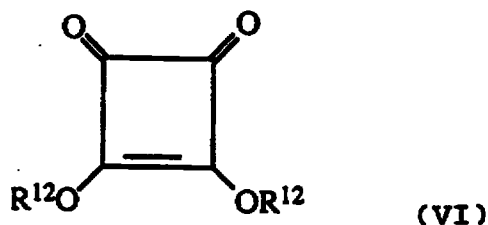
wherein X, R² and R¹² are as defined above or a salt or protected form thereof with a compound of formula



wherein R¹ is as defined in above and removing any protecting group to give a corresponding compound of formula I or a salt thereof;

or

c) reacting a compound of formula (VI)



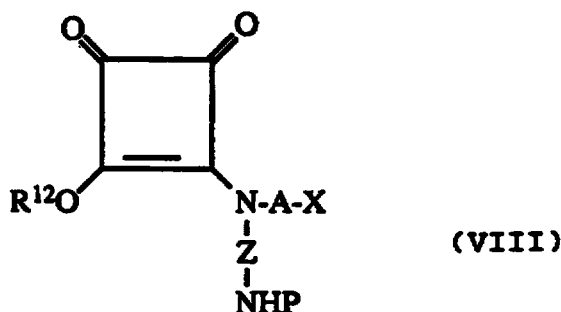
wherein R¹² is as defined above and each is the same or different, with a compound of formula



wherein X is as defined in above or a salt or protected form thereof, Z and A are as defined in above if required removing any protecting group; to give a corresponding compound having formula (I) wherein R¹ and R² taken together are Z, A and X are as defined above;

or

d) deprotecting, selectively if required, and cyclising a compound of formula (VIII)

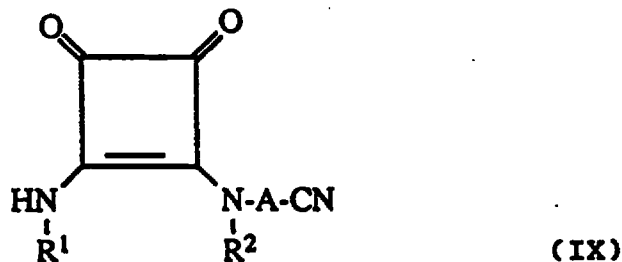


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wherein X, Z, R¹² and A are as defined above or a salt or protected form thereof, and P is an amino protecting group, which is preferably selectively removable if X is protected, to give a corresponding compound having formula I where R¹ and R² are Z if required also removing any protecting group on X;



or
e) reacting a compound of formula (IX)



15 wherein R^1 , R^2 and A are as defined in above with an azide, to give a corresponding compound of formula I where X is 5-tetrazolyl;

or

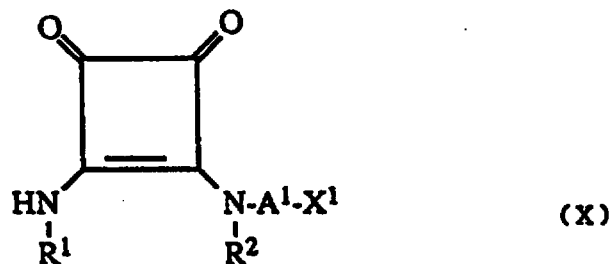
f) converting a compound of formula I wherein R^3 , R^4 and R^5 are alkyl groups to give a compound of formula I wherein R^3 , R^4 and R^5 are hydrogen or a salt thereof;

or

g) acidifying a salt of a compound of formula I to give the free acid or basifying an acid of formula I to give a salt thereof;

or

h) thermolysing a compound of formula (X)



35 wherein R^1 is as defined above, X^1 is CO_2R^3 or $-\text{PO}(\text{OR}^4)(\text{OR}^5)$ where R^3 , R^4 and R^5 are all alkyl; 3,5-dioxo-1,2,4-oxadiazolidin-2-yl or protected 5-tetrazolyl, and $-A^1-$ represents alkylene of 2 to 6 carbon atoms substituted by a $\text{S}(\text{O})_m$ aryl radical where m represents 1 or 2, if required removing any protecting group to give a corresponding compound of formula I wherein A is alkenylene of 2 to 6 carbon atoms.

40 2. A process as claimed in Claim 1 in which R^1 and R^2 are, independently, hydrogen, methyl, allyl, methallyl or benzyl or R^1 and R^2 taken together are $-\text{CH}_2\text{CH}_2-$, $-\text{CH}_2\text{C}(\text{R}^6)(\text{R}^7)\text{CH}_2-$ or $-\text{CH}_2\text{C}(\text{R}^8)(\text{R}^9)-\text{C}(\text{R}^{10})(\text{R}^{11})\text{CH}_2-$, where R^6 , R^8 and R^{10} are independently, hydrogen, alkyl of 1 to 6 carbon atoms or hydroxyl and R^7 , R^9 and R^{11} are, independently, hydrogen or alkyl of 1 to 6 carbon atoms.

3. A process as claimed in Claim 1 or Claim 2 where A is alkylene of 1 to 4 carbon atoms or trans-2-butenylene.

50 4. A process as claimed in any one of Claims 1 to 3 wherein X is carboxyl, phosphonyl or 5-tetrazolyl.

5. A process as claimed in Claim 1 in which the product is: N-(2-amino-3,4-dioxo-1-cyclobuten-1-yl)beta-alanine;

N-(2-amino-3,4-dioxo-1-cyclobutenyl)glycine ethyl ester;

55 2-[2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]-1,2,4-oxadiazolidine-3,5-dione;

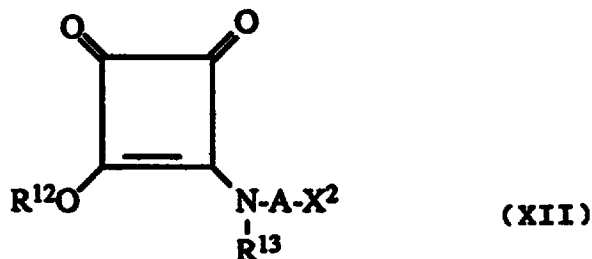
N-[2-(methylamino)-3,4-dioxo-1-cyclobutenyl]beta-alanine;

N-(2-amino-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)glycine;

N-(2-amino-3,4-dioxo-1-cyclobutenyl)-N-(2-methyl-2-propenyl)glycine acid;



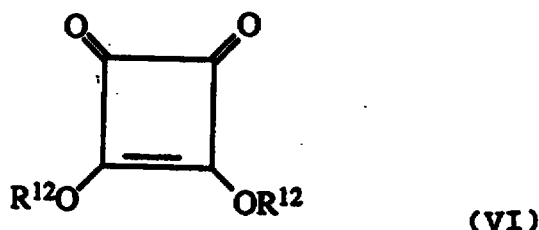
- [2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid;
 [[(2-amino-3,4-dioxo-1-cyclobutenyl)amino]methyl]phosphonic acid;
 [3-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]phosphonic acid;
 [4-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]phosphonic acid;
 5 [(E)-4-[(2-amino-3,4-dioxo-1-cyclobutenyl-1-yl)amino]-2-butenyl]phosphonic acid;
 [2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid;
 [[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]methyl]phosphonic acid;
 [2-(7,8-dioxo-2,5-diazabicyclo[4.2.0]-oct-1(6)-en-2-yl)ethyl]phosphonic acid;
 [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid;
 10 [2-(4-hydroxy-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid;
 [2-(4,4-dimethyl-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid;
 [3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)propyl]phosphonic acid;
 [(E)-3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-1-propenyl]-phosphonic acid;
 8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-ene-2-acetic acid;
 15 3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)propanoic acid;
 2-[(1H-tetrazol-5-yl)methyl]-2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione;
 2-[2-(1H-tetrazol-5-yl)ethyl]-2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione;
 N-(2-amino-3,4-dioxo-1-cyclobutenyl)glycine;
 4-[2-amino-3,4-dioxo-1-cyclobutenyl]amino]butanoic acid;
 20 3-[[3,4-dioxo-2-[(phenylmethyl)amino]-1-cyclobutenyl]amino]propanoic acid;
 N-(2-amino-3,4-dioxo-1-cyclobutenyl)-N-(phenylmethyl)glycine; or
 [2-(9,10-dioxo-2,7-diazabicyclo[6.2.0]dec-1(8)-en-2-yl)ethyl]phosphonic acid;
 or a pharmaceutically acceptable salt thereof.
- 25 6. A process as claimed in any one of Claims 1 to 5 in which the product is obtained in the form of an alkali metal, alkaline earth metal or ammonium salt.
7. A process for preparing a pharmaceutical composition which comprises bringing a compound of formula I or a pharmaceutically acceptable salt thereof as defined in any one of Claims 1 to 6 and a
 30 pharmaceutically acceptable carrier into a form suitable for therapeutical administration.
8. A process for preparing a compound of general formula (XII):



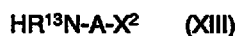
- or a salt thereof,
- 45 where X² represents CN, COOR¹⁴ where R¹⁴ is hydrogen, alkyl of 1 to 6 carbon atoms or a carboxyl protecting group, -PO(OR¹⁵)(OR¹⁶) where R¹⁵ and R¹⁶ are hydrogen or alkyl of 1 to 6 carbon atoms, 3,5-dioxo-1,2,4-oxadiazolidinyl or optionally protected 5-tetrazolyl; R¹² represents an alkoxy or aralkoxy leaving group and R¹³ represents hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, phenylalkyl of 7 to 12 carbon atoms or NHP wherein P is an amino protecting group and A is
 50 alkylene of 1 to 6 carbon atoms or alkenylene of 2 to 6 carbon atoms and Z are as defined in Claim 1 which comprises



a) reacting a compound of formula (VI)

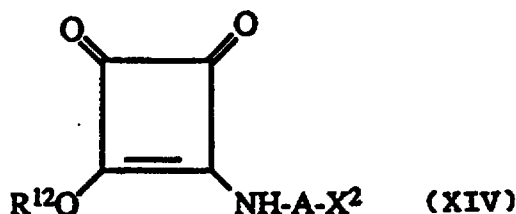


with a compound of formula



where A, R^{12} , R^{13} and X^2 are as defined in above to give a corresponding compound of formula XII;
or

b) N-alkylating a compound of formula XIV:



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where R^{12} , A and X^2 are as defined above in the presence of a strong base, with a compound of formula $\text{R}^2\text{-halo}$ where halo is a halogen and R^2 is as defined above except hydrogen to give a corresponding compound of formula (XII).

35

9. A process as claimed in Claim 8 wherein R^{13} is hydrogen, methyl, alkyl, methallyl or benzyl.

10. A process as claimed in Claim 8 wherein P is benzyloxycarbonyl or a substituted derivative thereof.

11. A process as claimed in anyone of Claims 8 to 10 wherein R^{12} is methyl or ethyl.

40

12. A process as claimed in any one of Claims 9 to 12 wherein R^{14} , R^{15} and R^{16} are selected from methyl and ethyl.

13. A process as claimed in Claim 9 in which the product is one of the following:

45

[2-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid, diethyl ester;

[[2-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]methyl]phosphonic acid, diethyl ester;

[3-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]phosphonic acid, diethyl ester;

[4-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]phosphonic acid, diethyl ester;

[(E)-4-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-butenyl]phosphonic acid diethyl ester;

[2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid diethyl ester;

50

[[2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)methylamino]methyl]phosphonic acid diethyl ester;

[3-[[2-(diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid phenylmethyl ester;

[3-[[2-(diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-hydroxypropyl]carbamic acid 1,1-dimethylethyl ester;

55

[3-[[1,1-Dimethylethylloxycarbonyl)methyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid phenylmethyl ester;

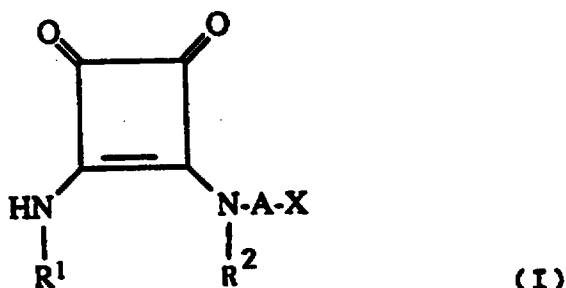
[3-[(Cyanomethyl)-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid 1,1-dimethylethyl ester; or



[4-[[2-(Diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]carbamic acid 1,1-dimethyl ethyl ester.

Claims for the following Contracting State : GR

1. A process for preparing a compound of the formula:



in which

R¹ is hydrogen, alkyl of 1 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms;

R² is hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms;

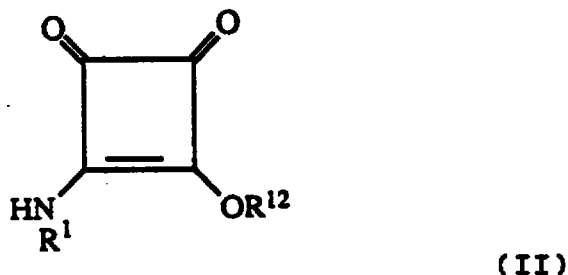
or

R¹ and R² taken together are Z where Z is -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- or -CH₂C(R⁸)(R⁹)-C(R¹⁰)-(R¹¹)CH₂-, where R⁶, R⁸ and R¹⁰ are, independently, hydrogen, alkyl of 1 to 6 carbon atoms or hydroxyl and R⁷, R⁹ and R¹¹ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms,

A is alkylene of 1 to 6 carbon atoms or alkenylene of 2 to 6 carbon atoms;

X is CO₂R³ in which R³ is hydrogen or alkyl of 1 to 6 carbon atoms, P(O)(OR⁴)(OR⁵) in which R⁴ and R⁵ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms, 3,5-dioxo-1,2,4-oxadiazolidin-2-yl or 5-tetrazolyl; or a pharmaceutically acceptable salt thereof, which comprises one of the following:

a) reacting a compound of formula (II)



herein R¹ is as defined in above and OR¹² represents any alkoxy or aralkoxy leaving group, with a compound of formula (III):

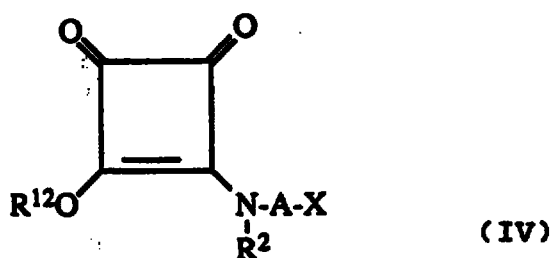
HNR²-A-X (III)

wherein R², A and X are as defined in above or a salt or protected form thereof, if required removing any protecting group; to give a compound of formula I wherein R² is as defined in above if desired isolating as a pharmaceutically acceptable salt;

or



b) reacting a compound of formula (IV)

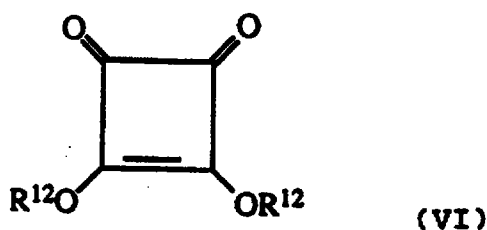


wherein X, R² and R¹² are as defined above or a salt or protected form thereof with a compound of formula



wherein R¹ is as defined in above and removing any protecting group to give a corresponding compound of formula I or a salt thereof;
or

c) reacting a compound of formula (VI)



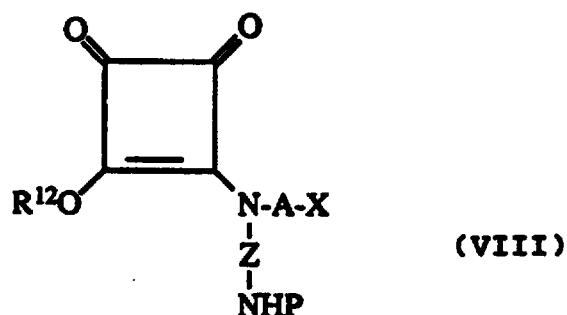
wherein R¹² is as defined above and each is the same or different, with a compound of formula



wherein X is as defined in above or a salt or protected form thereof, Z and A are as defined in above if required removing any protecting group; to give a corresponding compound having formula (I) wherein R¹ and R² taken together are Z, A and X are as defined above;

or

d) deprotecting, selectively if required, and cyclising a compound of formula (VIII)

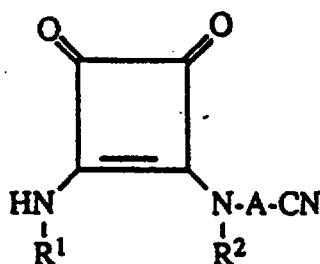


wherein X, Z, R¹² and A are as defined above or a salt or protected form thereof, and P is an amino protecting group, which is preferably selectively removable if X is protected, to give a corresponding compound having formula I where R¹ and R² are Z if required also removing any protecting group on X;



or

e) reacting a compound of formula (IX)



(IX)

wherein R^1 , R^2 and A are as defined in above with an azide, to give a corresponding compound of formula I where X is 5-tetrazolyl;

or

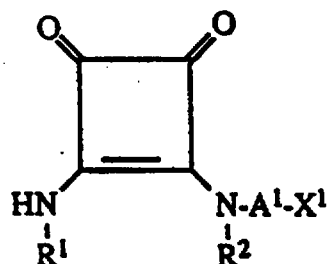
f) converting a compound of formula I wherein R^3 , R^4 and R^5 are alkyl groups to give a compound of formula I wherein R^3 , R^4 and R^5 are hydrogen or a salt thereof;

or

g) acidifying a salt of a compound of formula I to give the free acid of basifying an acid of formula I to give a salt thereof;

or

h) thermolysing a compound of formula (X)



(X)

wherein R^1 is as defined above, X^1 is CO_2R^3 or $-PO(OR^4)(OR^5)$ where R^3 , R^4 and R^5 are all alkyl; 3,5-dioxo-1,2,4-oxadiazolidin-2-yl or protected 5-tetrazolyl, and $-A^1-$ represents alkylene of 2 to 6 carbon atoms substituted by a $S(O)_m$ aryl radical where m represents 1 or 2, if required removing any protecting group to give a corresponding compound of formula I wherein A is alkenylene of 2 to 6 carbon atoms.

2. A process as claimed in Claim 1 in which R^1 and R^2 are, independently, hydrogen, methyl, allyl, methallyl or benzyl or R^1 and R^2 taken together are $-CH_2CH_2-$, $-CH_2C(R^6)(R^7)CH_2-$ or $-CH_2C(R^8)(R^9)-C(R^{10})(R^{11})CH_2-$, where R^6 , R^8 and R^{10} are independently, hydrogen, alkyl of 1 to 6 carbon atoms or hydroxyl and R^7 , R^9 and R^{11} are, independently, hydrogen or alkyl of 1 to 6 carbon atoms.

3. A process as claimed in Claim 1 or Claim 2 where A is alkylene of 1 to 4 carbon atoms or trans-2-butenylene.

4. A process as claimed in any one of Claims 1 to 3 wherein X is carboxyl, phosphonyl or 5-tetrazolyl.

5. A process as claimed in Claim 1 in which the product is: N-(2-amino-3,4-dioxo-1-cyclobuten-1-yl)beta-alanine;

N-(2-amino-3,4-dioxo-1-cyclobutenyl)glycine ethyl ester;

2-[2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]-1,2,4-oxadiazolidine-3,5-dione;

N-[2-(methylamino)-3,4-dioxo-1-cyclobutenyl]beta-alanine;

N-(2-amino-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)glycine;

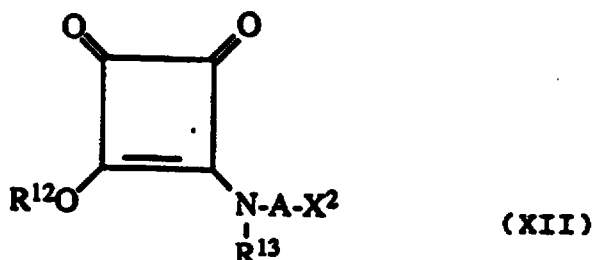
N-(2-amino-3,4-dioxo-1-cyclobutenyl)-N-(2-methyl-2-propenyl)glycine acid;

[2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid;



5 [[(2-amino-3,4-dioxo-1-cyclobutenyl)amino]methyl]phosphonic acid;
 [3-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]phosphonic acid;
 [4-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]phosphonic acid;
 [(E)-4-[(2-amino-3,4-dioxo-1-cyclobutenyl-1-yl)amino]-2-butenyl]phosphonic acid;
 10 [2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid;
 [[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]methyl]phosphonic acid;
 [2-(7,8-dioxo-2,5-diazabicyclo[4.2.0] -oct-1(6)-en-2-yl)ethyl]phosphonic acid;
 [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid;
 [2-(4-hydroxy-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid;
 15 [2-(4,4-dimethyl-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid;
 [3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)propyl]phosphonic acid;
 [(E)-3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-1-propenyl]-phosphonic acid;
 8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-ene-2-acetic acid;
 3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)propanoic acid;
 20 2-[(1H-tetrazol-5-yl)methyl]-2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione;
 2-[2-(1H-tetrazol-5-yl)ethyl]-2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione;
 N-(2-amino-3,4-dioxo-1-cyclobutenyl)glycine;
 4-[2-amino-3,4-dioxo-1-cyclobutenyl]amino]butanoic acid;
 3-[[3,4-dioxo-2-[(phenylmethyl)amino]-1-cyclobutenyl]amino]propanoic acid;
 25 N-(2-amino-3,4-dioxo-1-cyclobutenyl)-N-(phenylmethyl)glycine; or [2-(9,10-dioxo-2,7-diazabicyclo[6.2.0]-
 dec-1(8)-en-2-yl)ethyl]phosphonic acid;
 or a pharmaceutically acceptable salt thereof.

- 25 6. A process as claimed in any one of Claims 1 to 5 in which the product is obtained in the form of an alkali metal, alkaline earth metal or ammonium salt.
- 30 7. A process for preparing a pharmaceutical composition which comprises bringing a compound of formula I or a pharmaceutically acceptable salt thereof as defined in any one of Claims 1 to 6 and a pharmaceutically acceptable carrier into a form suitable for therapeutical administration.
8. A compound of general formula (XII):



45 or a salt thereof,
 where X² represents CN, COOR¹⁴ where R¹⁴ is hydrogen, alkyl of 1 to 6 carbon atoms or a carboxyl protecting group, -PO(OR¹⁵)(OR¹⁶) where R¹⁵ and R¹⁶ are hydrogen or alkyl of 1 to 6 carbon atoms, 3,5-dioxo-1,2,4-oxadiazolidinyl or optionally protected 5-tetrazolyl; R¹² represents an alkoxy or aralkoxy leaving group and R¹³ represents hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms, phenylalkyl of 7 to 12 carbon atoms or NHP wherein p is an amino protecting group and A is alkylene of 1 to 6 carbon atoms or alkenylene of 2 to 6 carbon atoms and Z are as defined in Claim 1.

- 50 9. A compound as claimed in Claim 8 wherein R¹³ is hydrogen, methyl, alkyl, methallyl or benzyl.
- 55 10. A compound as claimed in Claim 8 wherein P is benzyloxycarbonyl or a substituted derivative thereof.
11. A compound as claimed in anyone of Claims 8 to 10 wherein R¹² is methyl or ethyl.



12. A compound as claimed in any one of Claims 9 to 11 wherein R¹⁴, R¹⁵ and R¹⁶ are selected from methyl and ethyl.

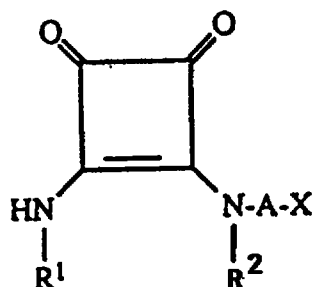
13. A compound as claimed in Claim 9 which is one of the following:

- 5 [2-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid, diethyl ester;
 [[2-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]methyl]phosphonic acid, diethyl ester;
 [3-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]phosphonic acid, diethyl ester;
 [4-[(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]phosphonic acid, diethyl ester;
 [(E)-4-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-butenyl]phosphonic acid diethyl ester;
 10 [2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid diethyl ester;
 [[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)methylamino]methyl]phosphonic acid diethyl ester;
 [3-[[2-(diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid
 phenylmethyl ester;
 [3-[[2-(diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]-2-hydroxypropyl]carbamic
 15 acid 1,1-dimethylethyl ester;
 [3-[[[(1,1-Dimethylethoxy)carbonyl]methyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic
 acid phenylmethyl ester;
 [3-[(Cyanomethyl)-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]carbamic acid 1,1-dimethylethyl
 ester; or [4-[[2-(Diethoxyphosphinyl)ethyl](2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]carbamic
 20 acid 1,1-dimethyl ethyl ester.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE

25 1. Verbindung der Formel



(I)

worin

40 R¹ Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Phenylalkyl mit 7 bis 12 Kohlenstoffatomen ist;

R² Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkenyl mit 2 bis 6 Kohlenstoffatomen oder Phenylalkyl mit 7 bis 12 Kohlenstoffatomen ist;

oder

45 R¹ und R² zusammen Z sind, worin Z für -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- oder -CH₂C(R⁸)(R⁹)-C(R¹⁰)-(R¹¹)CH₂- steht, worin R⁶, R⁸ und R¹⁰ unabhängig voneinander Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Hydroxyl bedeuten und R⁷, R⁹ und R¹¹ unabhängig voneinander Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen bedeuten,

A Alkylen mit 1 bis 6 Kohlenstoffatomen oder Alkenylen mit 2 bis 6 Kohlenstoffatomen ist;

50 X für CO₂R³, worin R³ für Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen, P(O)(OR⁴)(OR⁵), worin R⁴ und R⁵ unabhängig voneinander Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen bedeuten, 3,5-Dioxo-1,2,4-oxadiazolidin-2-yl oder 5-Tetrazolyl steht; oder ein pharmazeutisch akzeptables Salz davon.

55 2. Verbindung nach Anspruch 1, worin R¹ und R² unabhängig voneinander Wasserstoff, Methyl, Allyl, Methallyl oder Benzyl bedeuten oder R¹ und R² zusammen für -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- oder -CH₂C(R⁸)(R⁹)-C(R¹⁰)(R¹¹)CH₂- stehen, worin R⁶, R⁸ und R¹⁰ unabhängig voneinander Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Hydroxyl bedeuten und R⁷, R⁹ und R¹¹ unabhängig

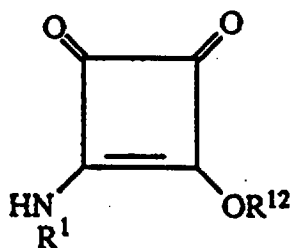


voneinander Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen bedeuten.

3. Verbindung nach Anspruch 1 oder Anspruch 2, worin A Alkylen mit 1 bis 4 Kohlenstoffatomen oder trans-2-Butenylen ist.
- 5 4. Verbindung nach einem der Ansprüche 1 bis 3, worin X Carboxyl, Phosphonyl oder 5-Tetrazolyl ist.
5. Verbindung nach Anspruch 1, welche eine der folgenden:
 - N-(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-beta-alanin,
 - 10 N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-glycinethylester;
 - 2-[2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-ethyl]-1,2,4-oxadiazolidin-3,5-dion;
 - N-[2-(Methylamino)-3,4-dioxo-1-cyclobutenyl]-betaalanin;
 - N-(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)-glycin;
 - N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-N-(2-methyl-2-propenyl)-glycin;
 - 15 [[2-Amino-3,4-dioxo-1-cyclobutenyl)-amino]-methyl]-phosphonsäure;
 - [3-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-phosphonsäure;
 - [4-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-butyl]-phosphonsäure;
 - [(E)-4-[(2-Amino-3,4-dioxo-1-cyclobutenyl-1-yl)-amino]-2-butenyl]-phosphonsäure;
 - [[2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-methyl]-phosphonsäure;
 - 20 [(E)-3-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-1-propenyl]-phosphonsäure;
 - 2-[2-(1H-Tetrazol-5-yl)-ethyl]-2,6-diazabicyclo[5.2.0]non-1(7)-en-8,9-dion;
 - N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-glycin;
 - 4-[(2-Amino-3,4-dioxo-1-cyclobutenyl)-amino]-butansäure;
 - 3-[[3,4-Dioxo-2-[(phenylmethyl)-amino]-1-cyclobutenyl]-amino]-propansäure; oder
 - 25 N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-N-(phenylmethyl)-glycin; oder ein pharmazeutisch akzeptables Salz davon ist.
6. Verbindung nach Anspruch 1, welche
 - 30 [2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-ethyl]-phosphonsäure oder ein pharmazeutisch akzeptables Salz davon;
 - [2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-ethyl]-phosphonsäure oder ein pharmazeutisch akzeptables Salz davon;
 - [2-(7,8-Dioxo-2,5-diazabicyclo[4.2.0])-oct-1(6)-en-2-yl)-ethyl]-phosphonsäure oder ein pharmazeutisch akzeptables Salz davon;
 - 35 [2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]-non-1(7)-en-2-yl)-ethyl]-phosphonsäure oder ein pharmazeutisch akzeptables Salz davon;
 - [2-(4-Hydroxy-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-phosphonsäure oder ein pharmazeutisch akzeptables Salz davon;
 - 40 [2-(4,4-Dimethyl-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-phosphonsäure oder ein pharmazeutisch akzeptables Salz davon;
 - 2-[3-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-propyl]-phosphonsäure oder ein pharmazeutisch akzeptables Salz davon;
 - 8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-essigsäure oder ein pharmazeutisch akzeptables Salz davon;
 - 45 3-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-propansäure oder ein pharmazeutisch akzeptables Salz davon;
 - 2-[(1H-Tetrazol-5-yl)-methyl]-2,6-diazabicyclo[5.2.0]non-1(7)-en-8,9-dion oder ein pharmazeutisch akzeptables Salz davon; oder
 - 50 [2-(9,10-Dioxo-2,7-diazabicyclo[6.2.0]-dec-1(8)-en-2-yl)-ethyl]-phosphonsäure oder ein pharmazeutisch akzeptables Salz davon ist.
7. Verbindung nach einem der Ansprüche 1 bis 6 in Form eines Alkalimetalls, Erdalkalimetalls oder Ammoniumsalzes.
8. Verfahren zur Herstellung einer Verbindung der Formel I, wie in Anspruch 1 definiert, welches umfaßt:



a) die Umsetzung einer Verbindung der Formel (II)



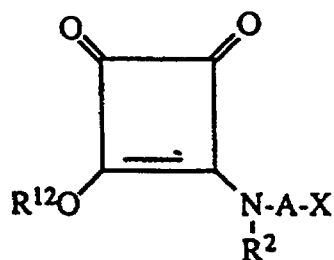
, (II)

worin R¹ die in Anspruch 1 angegebene Bedeutung hat und OR¹² jegliche austretende Alkoxy- oder Aralkoxygruppe darstellt, mit einer Verbindung der Formel (III):



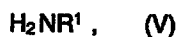
worin R², A und X die in Anspruch 1 angegebene Bedeutung haben, oder einem Salz oder einer geschützten Form davon, wobei, falls erforderlich, jegliche Schutzgruppe entfernt wird; zum Erhalt einer Verbindung der Formel I, worin R² die in Anspruch 1 angegebene Bedeutung hat, die gewünschtenfalls als pharmazeutisch akzeptables Salz isoliert wird; oder

b) die Umsetzung einer Verbindung der Formel (IV)



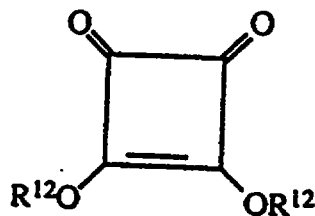
, (IV)

worin X, R² und R¹² die obige Bedeutung haben, oder eines Salzes oder einer geschützten Form davon, mit einer Verbindung der Formel



worin R¹ die in Anspruch 1 angegebene Bedeutung hat, und Entfernung jeglicher Schutzgruppe zum Erhalt einer entsprechenden Verbindung der Formel I oder eines Salzes davon; oder

c) die Umsetzung einer Verbindung der Formel (VI)



, (VI)

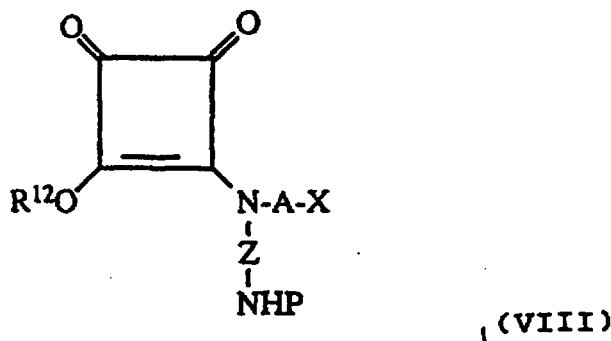
worin R¹² die obige Bedeutung hat und jedes gleich oder verschieden ist, mit einer Verbindung der Formel



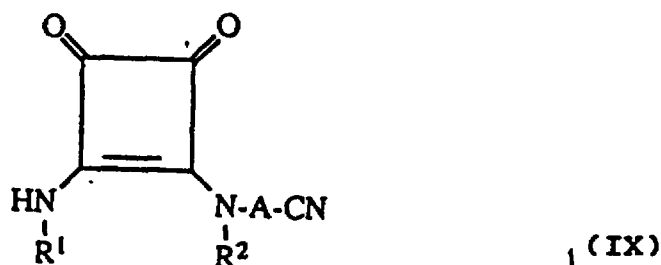
worin X die in Anspruch 1 angegebene Bedeutung hat, oder einem Salz oder einer geschützten Form davon, Z und A die in Anspruch 1 angegebene Bedeutung haben, wobei erforderlichenfalls



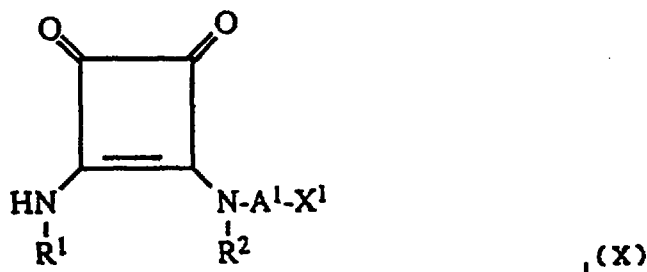
jegliche Schutzgruppe entfernt wird; zum Erhalt einer entsprechenden Verbindung mit der Formel (I), worin R^1 und R^2 zusammen Z sind, A und X die obige Bedeutung haben; oder
d) das, nötigenfalls selektive, Entschützen und Cyclisieren einer Verbindung der Formel (VIII)



worin X, Z, R^{12} und A die obige Bedeutung haben, oder ein Salz oder eine geschützte Form davon sind und P eine Aminoschutzgruppe ist, welche vorzugsweise selektiv entfernbar ist, wenn X geschützt ist, zum Erhalt einer entsprechenden Verbindung mit der Formel I, worin R^1 und R^2 Z sind, wobei nötigenfalls auch jegliche Schutzgruppe an X entfernt wird; oder
e) die Umsetzung einer Verbindung der Formel (IX)



worin R^1 , R^2 und A die in Anspruch 1 angegebene Bedeutung haben, mit einem Azid zum Erhalt einer entsprechenden Verbindung der Formel I, worin X für 5-Tetrazolyl steht; oder
f) das Überführen einer Verbindung der Formel I, worin R^3 , R^4 und R^5 Alkylgruppen sind, zum Erhalt einer Verbindung der Formel I, worin R^3 , R^4 und R^5 Wasserstoff sind, oder eines Salzes davon; oder
g) das Ansäuern eines Salzes einer Verbindung der Formel I zum Erhalt der freien Säure, oder Basischmachen einer Säure der Formel I zum Erhalt eines Salzes davon; oder
h) die Thermolyse einer Verbindung der Formel (X)

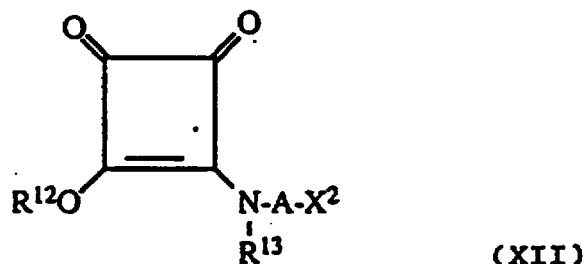


worin R^1 die obige Bedeutung hat, X^1 für CO_2R^3 oder $-PO(OR^4)(OR^5)$ steht, worin R^3 , R^4 und R^5 alle Alkyl, 3,5-Dioxo-1,2,4-oxadiazolidin-2-yl oder geschütztes 5-Tetrazolyl bedeuten und $-A^1-$ Alkylen mit 2 bis 6 Kohlenstoffatomen, substituiert durch eine $S(O)_m$ -Arylgruppe, worin m für 1 oder 2 steht, darstellt, wobei nötigenfalls jegliche Schutzgruppe zum Erhalt einer entsprechenden Verbindung der Formel I, worin A Alkenylen mit 2 bis 6 Kohlenstoffatomen ist, entfernt wird.



9. Pharmazeutische Zusammensetzung umfassend eine Verbindung der Formel I oder ein pharmazeutisch akzeptables Salz davon nach einem der Ansprüche 1 bis 7 und einen pharmazeutisch akzeptablen Träger.

- 5 10. Verbindung der allgemeinen Formel (XII):

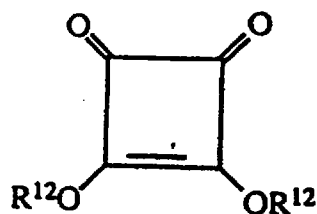


oder ein Salz davon,
 worin X^2 CN, COOR¹⁴, worin R¹⁴ Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder eine Carboxyl-Schutzgruppe, -PO(OR¹⁵)(OR¹⁶), worin R¹⁵ und R¹⁶ Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen sind, 3,5-Dioxo-1,2,4-oxadiazolidinyl oder gegebenenfalls geschütztes 5-Tetrazolyl bedeuten; R¹² eine austretende Alkoxy- oder Aralkoxygruppe darstellt und R¹³ Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkenyl mit 2 bis 6 Kohlenstoffatomen, Phenylalkyl mit 7 bis 12 Kohlenstoffatomen oder NHP darstellt, worin P eine Amino-Schutzgruppe ist und A und Z die in Anspruch 1 angegebene Bedeutung haben.

- 25 11. Verbindung nach Anspruch 10, worin R¹³ Wasserstoff, Methyl, Alkyl, Methallyl oder Benzyl ist.
12. Verbindung nach Anspruch 10, worin P Benzyloxycarbonyl oder ein substituiertes Derivat davon ist.
- 30 13. Verbindung nach einem der Ansprüche 10 bis 12, worin R¹² Methyl oder Ethyl ist.
14. Verbindung nach einem der Ansprüche 11 bis 13, worin R¹⁴, R¹⁵ und R¹⁶ ausgewählt sind aus Methyl und Ethyl.
- 35 15. Verbindung nach Anspruch 11, welche eine der folgenden:
 [2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-ethyl]-phosphonsäure-diethylester;
 [[2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-methyl]-phosphonsäure-diethylester;
 [3-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-phosphonsäure-diethylester;
 [4-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-butyl]-phosphonsäure-diethylester;
 40 [(E)-4-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-2-butenyl]-phosphonsäure-diethylester;
 [2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-ethyl]-phosphonsäure-diethylester;
 [[2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-methyl]-phosphonsäure-diethylester;
 [3-[[2-(Diethoxyphosphinyl)-ethyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-carbaminsäure-phenylmethylester;
 45 [3-[[2-(Diethoxyphosphinyl)-ethyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-2-hydroxypropyl]-carbaminsäure-1,1-dimethylethylester;
 [3-[[1,1-Dimethylethylloxycarbonyl]-methyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-carbaminsäure-phenylmethylester;
 [3-[(Cyanomethyl)-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-carbaminsäure-1,1-dimethylethylester; oder [4-[[2-(Diethoxyphosphinyl)-ethyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-butyl]-carbaminsäure-1,1-dimethylethylester ist.
- 50 16. Verfahren zur Herstellung einer Verbindung der Formel XII, wie in Anspruch 11 gezeigt und definiert, welche umfaßt:
- 55



a) die Umsetzung einer Verbindung der Formel (VI)



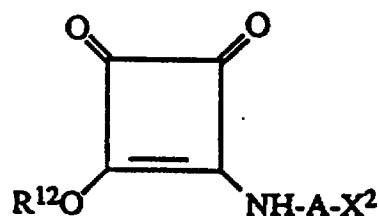
(VI)

mit einer Verbindung der Formel

$\text{HR}^{13}\text{N-A-X}^2$, (XIII)

worin A, R^{12} , R^{13} und X^2 die in Anspruch 11 angegebene Bedeutung haben, zum Erhalt einer entsprechenden Verbindung der Formel XII;
oder

b) die N-Alkylierung einer Verbindung der Formel XIV:

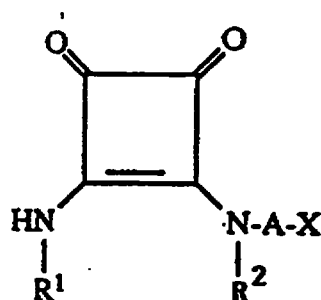


(XIV)

worin R^{12} , A und X^2 die obige Bedeutung haben, in Anwesenheit einer starken Base, mit einer Verbindung der Formel $\text{R}^2\text{-Halo}$, worin Halo ein Halogen bedeutet und R^2 die obige Bedeutung mit Ausnahme von Wasserstoff hat, zum Erhalt einer entsprechenden Verbindung der Formel (XII).

Patentansprüche für folgenden Vertragsstaat : ES

1. Verfahren zur Herstellung einer Verbindung der Formel



(I)

worin

R^1 Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Phenylalkyl mit 7 bis 12 Kohlenstoffatomen ist;

R^2 Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkenyl mit 2 bis 6 Kohlenstoffatomen oder Phenylalkyl mit 7 bis 12 Kohlenstoffatomen ist;

oder

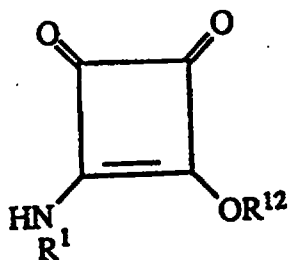


R¹ und R² zusammen Z sind, worin Z für -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- oder -CH₂C(R⁸)(R⁹)-C(R¹⁰)-(R¹¹)CH₂- steht, worin R⁶, R⁸ und R¹⁰ unabhängig voneinander Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Hydroxyl bedeuten und R⁷, R⁹ und R¹¹ unabhängig voneinander Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen bedeuten,

A Alkylen mit 1 bis 6 Kohlenstoffatomen oder Alkenylen mit 2 bis 6 Kohlenstoffatomen ist;

X für CO₂R³, worin R³ für Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen, P(O)(OR⁴)(OR⁵), worin R⁴ und R⁵ unabhängig voneinander Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen bedeuten, 3,5-Dioxo-1,2,4-oxadiazolidin-2-yl oder 5-Tetrazolyl steht; oder eines pharmazeutisch akzeptablen Salzes davon, welches eines von folgendem umfaßt:

a) Umsetzung einer Verbindung der Formel (II)



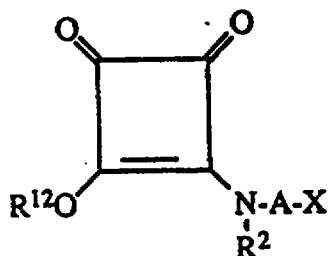
(II)

worin R¹ die oben angegebene Bedeutung hat und OR¹² jegliche austretende Alkoxy- oder Aralkoxygruppe darstellt, mit einer Verbindung der Formel (III):

HNR²-A-X, (III)

worin R², A und X die oben angegebene Bedeutung haben, oder einem Salz oder einer geschützten Form davon, wobei, falls erforderlich, jegliche Schutzgruppe entfernt wird; zum Erhalt einer Verbindung der Formel I, worin R² die oben angegebene Bedeutung hat, die gewünschtenfalls als pharmazeutisch akzeptables Salz isoliert wird; oder

b) die Umsetzung einer Verbindung der Formel (IV)



(IV)

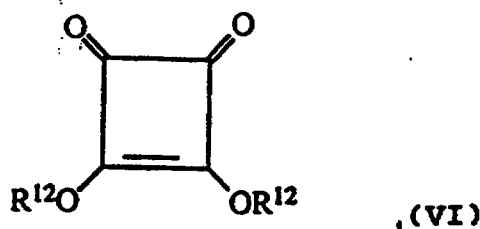
worin X, R² und R¹² die obige Bedeutung haben, oder eines Salzes oder einer geschützten Form davon, mit einer Verbindung der Formel

H₂NR¹, (V)

worin R¹ die in Anspruch 1 angegebene Bedeutung hat, und Entfernung jeglicher Schutzgruppe zum Erhalt einer entsprechenden Verbindung der Formel I oder eines Salzes davon; oder



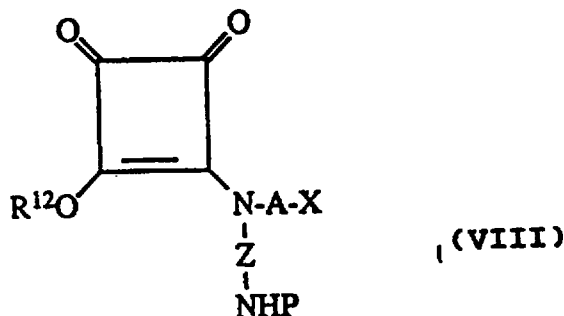
c) die Umsetzung einer Verbindung der Formel (VI)



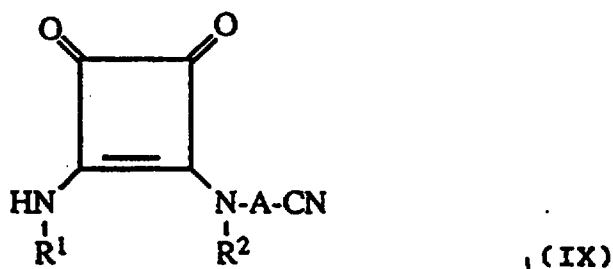
worin R¹² die obige Bedeutung hat und jedes gleich oder verschieden ist, mit einer Verbindung der Formel



worin X die oben angegebene Bedeutung hat, oder einem Salz oder einer geschützten Form davon, Z und A die oben angegebene Bedeutung haben, wobei erforderlichenfalls jegliche Schutzgruppe entfernt wird; zum Erhalt einer entsprechenden Verbindung mit der Formel (I), worin R¹ und R² zusammen Z sind, A und X die obige Bedeutung haben; oder
d) das, nötigenfalls selektive, Entschützen und Cyclisieren einer Verbindung der Formel (VIII)



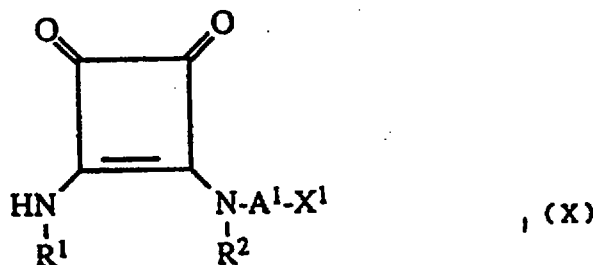
worin X, Z, R¹² und A die obige Bedeutung haben, oder ein Salz oder eine geschützte Form davon sind und P eine Aminoschutzgruppe ist, welche vorzugsweise selektiv entfernbar ist, wenn X geschützt ist, zum Erhalt einer entsprechenden Verbindung mit der Formel I, worin R¹ und R² Z sind, wobei nötigenfalls auch jegliche Schutzgruppe an X entfernt wird; oder
e) die Umsetzung einer Verbindung der Formel (IX)



worin R¹, R² und A die oben angegebene Bedeutung haben, mit einem Azid zum Erhalt einer entsprechenden Verbindung der Formel I, worin X für 5-Tetrazolyl steht; oder
f) das Überführen einer Verbindung der Formel I, worin R³, R⁴ und R⁵ Alkylgruppen sind, zum Erhalt einer Verbindung der Formel I, worin R³, R⁴ und R⁵ Wasserstoff sind, oder eines Salzes davon; oder
g) das Ansäuern eines Salzes einer Verbindung der Formel I zum Erhalt der freien Säure, oder Basischmachen einer Säure der Formel I zum Erhalt eines Salzes davon; oder



h) die Thermolyse einer Verbindung der Formel (X)



15 worin R¹ die obige Bedeutung hat, X¹ für CO₂R³ oder -PO(OR⁴)(OR⁵) steht, worin R³, R⁴ und R⁵ alle Alkyl, 3,5-Dioxo-1,2,4-oxadiazolidin-2-yl oder geschütztes 5-Tetrazolyl bedeuten und -A¹- Alkylen mit 2 bis 6 Kohlenstoffatomen, substituiert durch eine S(O)_m-Arylgruppe, worin m für 1 oder 2 steht, darstellt, wobei nötigenfalls jegliche Schutzgruppe zum Erhalt einer entsprechenden Verbindung der Formel I, worin A Alkenylen mit 2 bis 6 Kohlenstoffatomen ist, entfernt wird.

- 20 2. Verfahren nach Anspruch 1, worin R¹ und R² unabhängig voneinander Wasserstoff, Methyl, Allyl, Methallyl oder Benzyl bedeuten, oder R¹ und R² zusammen für -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- oder -CH₂C(R⁸)(R⁹)-C(R¹⁰)(R¹¹)CH₂- stehen, worin R⁶, R⁸ und R¹⁰ unabhängig voneinander Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Hydroxyl bedeuten und R⁷, R⁹ und R¹¹ unabhängig voneinander Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen bedeuten.
- 25 3. Verfahren nach Anspruch 1 oder Anspruch 2, worin A Alkylen mit 1 bis 4 Kohlenstoffatomen oder trans-2-Butenylen ist.
4. Verfahren nach einem der Ansprüche 1 bis 3, worin X Carboxyl, Phosphonyl oder 5-Tetrazolyl ist.
- 30 5. Verfahren nach Anspruch 1, worin das Produkt:
 N-(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-beta-alanin,
 N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-glycinethylester;
 2-[2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-ethyl]-1,2,4-oxadiazolidin-3,5-dion;
 N-[2-(Methylamino)-3,4-dioxo-1-cyclobutenyl]-betaalanin;
 35 N-(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)-glycin;
 N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-N-(2-methyl-2-propenyl)-glycinsäure;
 [2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-ethyl]-phosphonsäure;
 [(2-Amino-3,4-dioxo-1-cyclobutenyl)-amino]-methyl]-phosphonsäure;
 [3-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-phosphonsäure;
 40 [4-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-butyl]-phosphonsäure;
 [(E)-4-[(2-Amino-3,4-dioxo-1-cyclobutenyl-1-yl)-amino]-2-butenyl]-phosphonsäure;
 [2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-ethyl]-phosphonsäure;
 [(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-methyl]-phosphonsäure;
 [2-(7,8-Dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-yl)-ethyl]-phosphonsäure;
 45 [2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-phosphonsäure;
 [2-(4-Hydroxy-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-phosphonsäure;
 [2-(4,4-Dimethyl-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-phosphonsäure;
 [3-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-propyl]-phosphonsäure;
 [(E)-3-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-1-propenyl]-phosphonsäure;
 50 8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-essigsäure;
 3-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-propansäure;
 2-[(1H-Tetrazol-5-yl)-methyl]-2,6-diazabicyclo[5.2.0]non-1(7)-en-8,9-dion;
 2-[2-(1H-Tetrazol-5-yl)-ethyl]-2,6-diazabicyclo[5.2.0]non-1(7)-en-8,9-dion;
 N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-glycin;
 55 4-[(2-Amino-3,4-dioxo-1-cyclobutenyl)-amino]-butansäure;
 3-[[3,4-Dioxo-2-[(phenylmethyl)-amino]-1-cyclobutenyl]-amino]-propansäure;
 N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-N-(phenylmethyl)-glycin; oder
 [2-(9,10-Dioxo-2,7-diazabicyclo[6.2.0]dec-1(8)-en-2-yl)-ethyl]-phosphonsäure oder ein pharmazeutisch

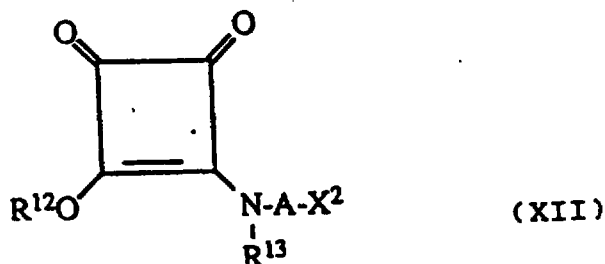


akzeptables Salz davon ist.

6. Verfahren nach einem der Ansprüche 1 bis 5, worin das Produkt in Form eines Alkalimetalls, Erdalkalimetalls oder Ammoniumsalzes erhalten wird.

7. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, bei welchem eine Verbindung der Formel I oder ein pharmazeutisch akzeptables Salz davon nach einem der Ansprüche 1 bis 6 und ein pharmazeutisch akzeptabler Träger in eine zur therapeutischen Verabreichung geeignete Form gebracht wird.

8. Verfahren zur Herstellung einer Verbindung der allgemeinen Formel (XII):

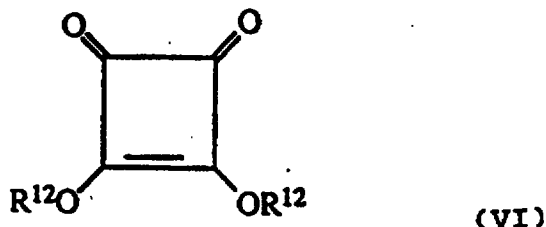


oder eines Salzes davon,

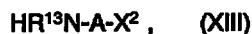
worin X^2 CN, COOR^{14} , worin R^{14} Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder eine Carboxyl-Schutzgruppe,

$-\text{PO}(\text{OR}^{15})(\text{OR}^{16})$, worin R^{15} und R^{16} Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen sind, 3,5-Dioxo-1,2,4-oxadiazolidinyl oder gegebenenfalls geschütztes 5-Tetrazolyl bedeuten; R^{12} eine austretende Alkoxy- oder Aralkoxygruppe darstellt und R^{13} Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkenyl mit 2 bis 6 Kohlenstoffatomen, Phenylalkyl mit 7 bis 12 Kohlenstoffatomen oder NHP darstellt, worin P eine Amino-Schutzgruppe ist und A Alkyl mit 1 bis 6 Kohlenstoffatomen oder Alkenyl mit 2 bis 6 Kohlenstoffatomen ist und Z die in Anspruch 1 angegebene Bedeutung hat, welches

a) die Umsetzung einer Verbindung der Formel (VI)



mit einer Verbindung der Formel

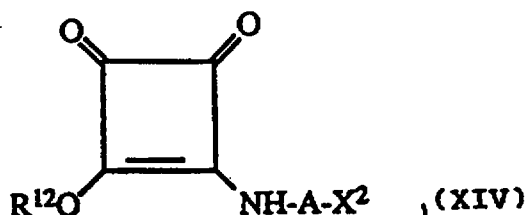


worin A, R^{12} , R^{13} und X^2 die oben angegebene Bedeutung haben, zum Erhalt einer entsprechenden Verbindung der Formel XII;

oder



b) die N-Alkylierung einer Verbindung der Formel XIV:

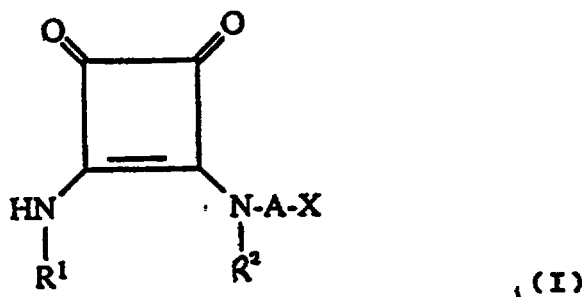


worin R^{12} , A und X^2 die obige Bedeutung haben, in Anwesenheit einer starken Base, mit einer Verbindung der Formel $\text{R}^2\text{-Halo}$, worin Halo ein Halogen bedeutet und R^2 die obige Bedeutung mit Ausnahme von Wasserstoff hat, zum Erhalt einer entsprechenden Verbindung der Formel (XII) umfaßt.

9. Verfahren nach Anspruch 8, worin R^{13} Wasserstoff, Methyl, Alkyl, Methallyl oder Benzyl ist.
10. Verfahren nach Anspruch 8, worin P Benzyloxycarbonyl oder ein substituiertes Derivat davon ist.
11. Verfahren nach einem der Ansprüche 8 bis 10, worin R^{12} Methyl oder Ethyl ist.
12. Verfahren nach einem der Ansprüche 9 bis 12, worin R^{14} , R^{15} und R^{16} ausgewählt sind aus Methyl und Ethyl.
13. Verfahren nach Anspruch 9, worin das Produkt eines von folgenden:
 - [2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-ethyl]-phosphonsäure-diethylester;
 - [[2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-methyl]-phosphonsäure-diethylester;
 - [3-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-phosphonsäure-diethylester;
 - [4-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-butyl]-phosphonsäure-diethylester;
 - [(E)-4-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-2-butenyl]-phosphonsäure-diethylester;
 - [2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-ethyl]-phosphonsäure-diethylester;
 - [[2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-methyl]-phosphonsäure-diethylester;
 - [3-[[2-(Diethoxyphosphinyl)-ethyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-carbaminsäure-phenylmethylester;
 - [3-[[2-(Diethoxyphosphinyl)-ethyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-2-hydroxypropyl]-carbaminsäure-1,1-dimethylethylester;
 - [3-[[1,1-Dimethylethoxyloxycarbonyl]-methyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-carbaminsäure-phenylmethylester;
 - [3-[(Cyanomethyl)-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-carbaminsäure-1,1-dimethylethylester; oder [4-[[2-(Diethoxyphosphinyl)-ethyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-butyl]-carbaminsäure-1,1-dimethylethylester ist.

Patentansprüche für folgenden Vertragsstaat : GR

1. Verfahren zur Herstellung einer Verbindung der Formel





worin

R¹ Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Phenylalkyl mit 7 bis 12 Kohlenstoffatomen ist;

R² Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkenyl mit 2 bis 6 Kohlenstoffatomen oder Phenylalkyl mit 7 bis 12 Kohlenstoffatomen ist;

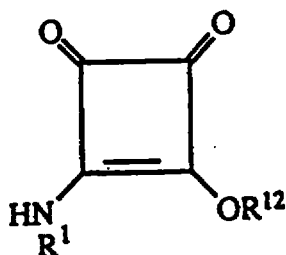
oder

R¹ und R² zusammen Z sind, worin Z für -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- oder -CH₂C(R⁸)(R⁹)-C(R¹⁰)-(R¹¹)CH₂- steht, worin R⁶, R⁸ und R¹⁰ unabhängig voneinander Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Hydroxyl bedeuten und R⁷, R⁹ und R¹¹ unabhängig voneinander Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen bedeuten,

A Alkyl mit 1 bis 6 Kohlenstoffatomen oder Alkenyl mit 2 bis 6 Kohlenstoffatomen ist;

X für CO₂R³, worin R³ für Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen, P(O)(OR⁴)(OR⁵), worin R⁴ und R⁵ unabhängig voneinander Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen bedeuten, 3,5-Dioxo-1,2,4-oxadiazolidin-2-yl oder 5-Tetrazolyl steht; oder eines pharmazeutisch akzeptablen Salzes davon, welches eines von folgendem umfaßt:

a) Umsetzung einer Verbindung der Formel (II)



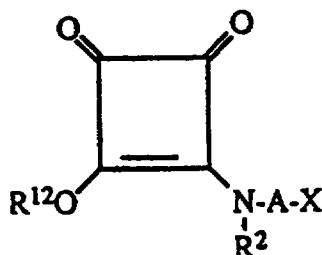
(II)

worin R¹ die oben angegebene Bedeutung hat und OR¹² jegliche austretende Alkoxy- oder Aralkoxygruppe darstellt, mit einer Verbindung der Formel (III):

HNR²-A-X, (III)

worin R², A und X die oben angegebene Bedeutung haben, oder einem Salz oder einer geschützten Form davon, wobei, falls erforderlich, jegliche Schutzgruppe entfernt wird; zum Erhalt einer Verbindung der Formel I, worin R² die oben angegebene Bedeutung hat, die gewünschtenfalls als pharmazeutisch akzeptables Salz isoliert wird; oder

b) die Umsetzung einer Verbindung der Formel (IV)



(IV)

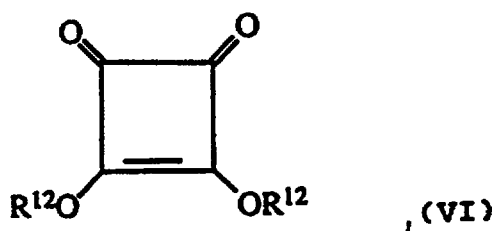
worin X, R² und R¹² die obige Bedeutung haben, oder eines Salzes oder einer geschützten Form davon, mit einer Verbindung der Formel

H₂NR¹, (V)

worin R¹ die oben angegebene Bedeutung hat, und Entfernung jeglicher Schutzgruppe zum Erhalt einer entsprechenden Verbindung der Formel I oder eines Salzes davon; oder



c) die Umsetzung einer Verbindung der Formel (VI)

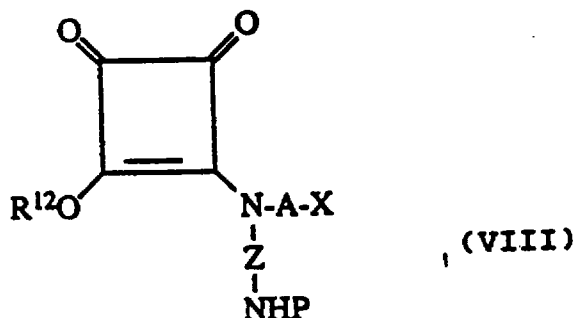


worin R^{12} die obige Bedeutung hat und jedes gleich oder verschieden ist, mit einer Verbindung der Formel

$\text{H}_2\text{N}-\text{Z}-\text{NH}-\text{A}-\text{X}$, (VII)

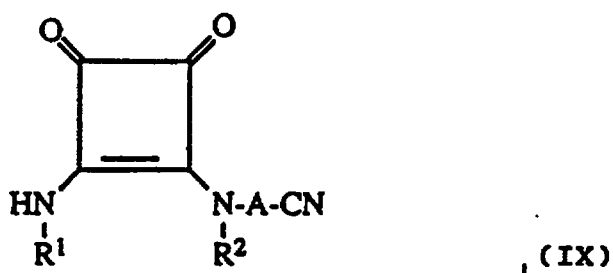
worin X die oben angegebene Bedeutung hat, oder einem Salz oder einer geschützten Form davon, Z und A die oben angegebene Bedeutung haben, wobei erforderlichenfalls jegliche Schutzgruppe entfernt wird; zum Erhalt einer entsprechenden Verbindung mit der Formel (I), worin R^1 und R^2 zusammen Z sind, A und X die obige Bedeutung haben; oder

d) das, nötigenfalls selektive, Entschützen und Cyclisieren einer Verbindung der Formel (VIII)



worin X, Z, R^{12} und A die obige Bedeutung haben, oder ein Salz oder eine geschützte Form davon sind und P eine Aminoschutzgruppe ist, welche vorzugsweise selektiv entfernbar ist, wenn X geschützt ist, zum Erhalt einer entsprechenden Verbindung mit der Formel I, worin R^1 und R^2 Z sind, wobei nötigenfalls auch jegliche Schutzgruppe an X entfernt wird; oder

e) die Umsetzung einer Verbindung der Formel (IX)



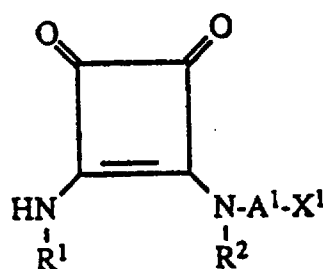
worin R^1 , R^2 und A die oben angegebene Bedeutung haben, mit einem Azid zum Erhalt einer entsprechenden Verbindung der Formel I, worin X für 5-Tetrazolyl steht; oder

f) das Überführen einer Verbindung der Formel I, worin R^3 , R^4 und R^5 Alkylgruppen sind, zum Erhalt einer Verbindung der Formel I, worin R^3 , R^4 und R^5 Wasserstoff sind, oder eines Salzes davon; oder

g) das Ansäuern eines Salzes einer Verbindung der Formel I zum Erhalt der freien Säure, oder Basischmachen einer Säure der Formel I zum Erhalt eines Salzes davon; oder



h) die Thermolyse einer Verbindung der Formel (X)



, (X)

worin R¹ die obige Bedeutung hat, X¹ für CO₂R³ oder -PO(OR⁴)(OR⁵) steht, worin R³, R⁴ und R⁵ alle Alkyl, 3,5-Dioxo-1,2,4-oxadiazolidin-2-yl oder geschütztes 5-Tetrazolyl bedeuten und -A¹- Alkylen mit 2 bis 6 Kohlenstoffatomen, substituiert durch eine S(O)_m-Arylgruppe, worin m für 1 oder 2 steht, darstellt, wobei nötigenfalls jegliche Schutzgruppe zum Erhalt einer entsprechenden Verbindung der Formel I, worin A Alkenylen mit 2 bis 6 Kohlenstoffatomen ist, entfernt wird.

2. Verfahren nach Anspruch 1, worin R¹ und R² unabhängig voneinander Wasserstoff, Methyl, Allyl, Methallyl oder Benzyl bedeuten oder R¹ und R² zusammen für -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- oder -CH₂C(R⁸)(R⁹)-C(R¹⁰)(R¹¹)CH₂- stehen, worin R⁶, R⁸ und R¹⁰ unabhängig voneinander Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder Hydroxyl bedeuten und R⁷, R⁹ und R¹¹ unabhängig voneinander Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen bedeuten.
3. Verfahren nach Anspruch 1 oder Anspruch 2, worin A Alkylen mit 1 bis 4 Kohlenstoffatomen oder trans-2-Butenylen ist.
4. Verfahren nach einem der Ansprüche 1 bis 3, worin X Carboxyl, Phosphonyl oder 5-Tetrazolyl ist.
5. Verfahren nach Anspruch 1, worin das Produkt:
 - N-(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-beta-alanin,
 - N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-glycinethylester;
 - 2-[2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-ethyl]-1,2,4-oxadiazolidin-3,5-dion;
 - N-[2-(Methylamino)-3,4-dioxo-1-cyclobutenyl]-betaalanin;
 - N-(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)-glycin;
 - N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-N-(2-methyl-2-propenyl)-glycinsäure;
 - [2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-ethyl]-phosphonsäure;
 - [(2-Amino-3,4-dioxo-1-cyclobutenyl)-amino]-methyl]-phosphonsäure;
 - [3-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-phosphonsäure;
 - [4-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-amino]-butyl]-phosphonsäure;
 - [(E)-4-[(2-Amino-3,4-dioxo-1-cyclobutenyl-1-yl)-amino]-2-butenyl]-phosphonsäure;
 - [2-[(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-ethyl]-phosphonsäure;
 - [(2-Amino-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-methyl]-phosphonsäure;
 - [2-(7,8-Dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-yl)-ethyl]-phosphonsäure;
 - [2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-phosphonsäure;
 - [2-(4-Hydroxy-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-phosphonsäure;
 - [2-(4,4-Dimethyl-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-ethyl]-phosphonsäure;
 - [3-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-propyl]-phosphonsäure;
 - [(E)-3-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-1-propenyl]-phosphonsäure;
 - 8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-essigsäure;
 - 3-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-propansäure;
 - 2-[(1H-Tetrazol-5-yl)-methyl]-2,6-diazabicyclo[5.2.0]non-1(7)-en-8,9-dion;
 - 2-[2-(1H-Tetrazol-5-yl)-ethyl]-2,6-diazabicyclo[5.2.0]non-1(7)-en-8,9-dion;
 - N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-glycin;
 - 4-[(2-Amino-3,4-dioxo-1-cyclobutenyl)-amino]-butansäure;
 - 3-[3,4-Dioxo-2-[(phenylmethyl)-amino]-1-cyclobutenyl]-amino]-propansäure;
 - N-(2-Amino-3,4-dioxo-1-cyclobutenyl)-N-(phenylmethyl)-glycin;



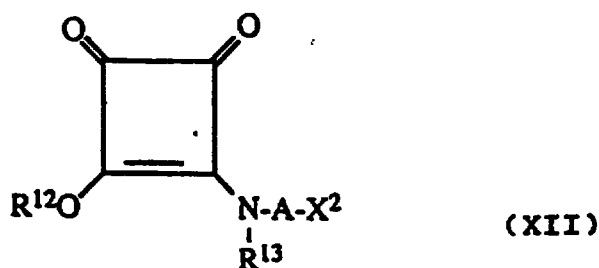
oder

[2-(9,10-Dioxo-2,7-diazabicyclo[6.2.0]-dec-1(8)-en-2-yl)-ethyl]-phosphonsäure oder ein pharmazeutisch akzeptables Salz davon ist.

- 5 6. Verfahren nach einem der Ansprüche 1 bis 5, worin das Produkt in Form eines Alkalimetalls, Erdalkalimetalls oder Ammoniumsalzes erhalten wird.
7. Verfahren zur Herstellung einer pharmazeutischen Zusammensetzung, bei welchem eine Verbindung der Formel I oder ein pharmazeutisch akzeptables Salz davon nach einem der Ansprüche 1 bis 6 und
10 ein pharmazeutisch akzeptabler Träger in eine zur therapeutischen Verabreichung geeignete Form gebracht wird.
8. Verbindung der allgemeinen Formel (XII):

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oder ein Salz davon,
worin X^2 CN, COOR¹⁴, worin R¹⁴ Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen oder eine Carboxyl-Schutzgruppe, -PO(OR¹⁵)(OR¹⁶), worin R¹⁵ und R¹⁶ Wasserstoff oder Alkyl mit 1 bis 6 Kohlenstoffatomen sind, 3,5-Dioxo-1,2,4-oxadiazolidinyl oder gegebenenfalls geschütztes 5-Tetrazolyl bedeuten; R¹² eine austretende Alkoxy- oder Aralkoxygruppe darstellt und R¹³ Wasserstoff, Alkyl mit 1 bis 6 Kohlenstoffatomen, Alkenyl mit 2 bis 6 Kohlenstoffatomen, Phenylalkyl mit 7 bis 12 Kohlenstoffatomen oder NHP darstellt, worin P eine Amino-Schutzgruppe ist und A Alkyl mit 1 bis 6 Kohlenstoffatomen oder Alkenyl mit 2 bis 6 Kohlenstoffatomen ist und Z die in Anspruch 1 angegebene Bedeutung hat.

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9. Verbindung nach Anspruch 8, worin R¹³ Wasserstoff, Methyl, Alkyl, Methallyl oder Benzyl ist.

10. Verbindung nach Anspruch 8, worin P Benzyloxycarbonyl oder ein substituiertes Derivat davon ist.

11. Verbindung nach einem der Ansprüche 8 bis 10, worin R¹² Methyl oder Ethyl ist.

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12. Verbindung nach einem der Ansprüche 9 bis 11, worin R¹⁴, R¹⁵ und R¹⁶ ausgewählt sind aus Methyl und Ethyl.

13. Verbindung nach Anspruch 9, welche eine der folgenden:

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[2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-ethyl]-phosphonsäure-diethylester;
[[2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-methyl]-phosphonsäure-diethylester;
[3-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-phosphonsäure-diethylester;
[4-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-butyl]-phosphonsäure-diethylester;
[(E)-4-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-2-butenyl]-phosphonsäure-diethylester;
[2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-ethyl]-phosphonsäure-diethylester;
50 [[2-[(2-Ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-methylamino]-methyl]-phosphonsäure-diethylester;
[3-[[2-(Diethoxyphosphinyl)-ethyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-carbaminsäure-phenylmethylester;
[3-[[2-(Diethoxyphosphinyl)-ethyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-2-hydroxypropyl]-carbaminsäure-1,1-dimethylethylester;
55 [3-[[[1,1-Dimethylethylloxycarbonyl]-methyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-carbaminsäurephenylmethylester;
[3-[(Cyanomethyl)-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-amino]-propyl]-carbaminsäure-1,1-dimethylethylester; oder [4-[[2-(Diethoxyphosphinyl)-ethyl]-(2-ethoxy-3,4-dioxo-1-cyclobuten-1-yl)-ami-

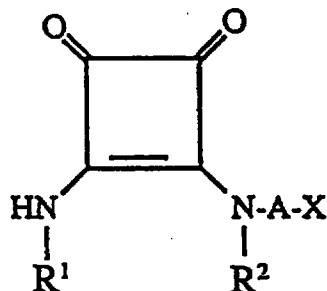


no]-butyl]-carbaminsäure-1,1-dimethylethylester
ist.

Revendications

5 Revendications pour les Etats contractants suivants : AT, BE, CH, DE, DK, FR, GB, IT, LI, LU, NL, PT, SE

1. Composé de formule (I) : où :



(I)

R¹ est hydrogène, alcoyle en 1 à 6 atomes de carbone ou phénylcoyle en 7 à 12 atomes de carbone;

R² est hydrogène, alcoyle en 1 à 6 atomes de carbone, alcényle en 2 à 6 atomes de carbone ou phénylcoyle en 7 à 12 atomes de carbone, ou

R¹ et R², pris ensemble, sont Z, qui est -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- ou -CH₂C(R⁸)(R⁹)-C(R¹⁰)-(R¹¹)CH₂-, où R⁶, R⁸ et R¹⁰ sont, indépendamment, hydrogène, alcoyle en 1 à 6 atomes de carbone ou hydroxyle, et R⁷, R⁹ et R¹¹ sont, indépendamment, hydrogène ou alcoyle en 1 à 6 atomes de carbone;

A est alcoylène en 1 à 6 atomes de carbone ou alcénylène en 2 à 6 atomes de carbone;

X est -CO₂R³ dans lequel R³ est hydrogène ou alcoyle en 1 à 6 atomes de carbone, -P(O)(OR⁴)-(OR⁵) dans lequel R⁴ et R⁵ sont, indépendamment, hydrogène ou alcoyle en 1 à 6 atomes de carbone, 3,5-dioxo-1,2,4-oxadiazolidin-2-yle ou 5-tétrazolylo, ou

un sel pharmaceutiquement acceptable de celui-ci.

2. Composé suivant la revendication 1, dans lequel R¹ et R² sont, indépendamment, hydrogène, méthyle, allyle, méthallyle ou benzyle ou, R¹ et R², pris ensemble, sont -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- ou -CH₂C(R⁸)(R⁹)-C(R¹⁰)(R¹¹)CH₂-, où R⁶, R⁸ et R¹⁰ sont, indépendamment, hydrogène, alcoyle en 1 à 6 atomes de carbone ou hydroxyle, et R⁷, R⁹ et R¹¹ sont, indépendamment, hydrogène ou alcoyle en 1 à 6 atomes de carbone.

3. Composé suivant la revendication 1 ou 2, dans lequel A est alcoylène en 1 à 4 atomes de carbone ou trans-2-buténylène.

4. Composé suivant l'une quelconque des revendications 1 à 3, dans lequel X est carboxyle, phosphonyle ou 5-tétrazolylo.

5. Composé suivant la revendication 1, qui est l'un des suivants :

la N-(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)bêta-alanine;

l'ester éthylique de la N-(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)glycine;

la 2-[2-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]éthyl]-1,2,4-oxadiazolidine-3,5-dione;

la N-[2-(méthylamino)-3,4-dioxo-1-cyclobutèn-1-yl)bêta-alanine;

la N-(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)-N-(2-propèn-1-yl)glycine;

la N-(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)-N-(2-méthyl-2-propèn-1-yl)glycine;

l'acide [[2-(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]méthyl]phosphonique;

l'acide [3-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]phosphonique;

l'acide [4-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]butyl]phosphonique;

l'acide [(E)-4-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]-2-butén-1-yl]phosphonique;

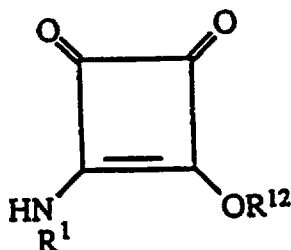
l'acide [2-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)méthylamino]méthyl]phosphonique;



- l'acide [(E)-3-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)-1-propèn-yl]phosphonique;
 la 2-[2-(1H-tétrazol-5-yl)éthyl]-2,6-diazabicyclo[5,2,0]non-1(7)-ène-8,9-dione;
 la N-(2-amino-3,4-dioxo-1-cyclobutèn-yl)glycine;
 l'acide 4-[2-amino-3,4-dioxo-1-cyclobutèn-yl]amino]butanoïque;
 l'acide 3-[3,4-dioxo-2-[(phénylméthyl)amino]-1-cyclobutèn-yl]amino]propanoïque, ou
 la N-(2-amino-3,4-dioxo-1-cyclobutèn-yl)-N-(phénylméthyl)glycine, ou un sel pharmaceutiquement acceptable de ceux-ci.
6. Composé suivant la revendication 1, qui est :
- l'acide [2-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]éthyl]phosphonique ou un sel pharmaceutiquement acceptable de celui-ci;
 l'acide [2-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)méthylamino]éthyl]phosphonique ou un sel pharmaceutiquement acceptable de celui-ci;
 l'acide [2-(7,8-dioxo-2,5-diazabicyclo[4,2,0]oct-1(6)-èn-2-yl)éthyl]phosphonique ou un sel pharmaceutiquement acceptable de celui-ci;
 l'acide [2-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)éthyl]phosphonique ou un sel pharmaceutiquement acceptable de celui-ci;
 l'acide [2-(4-hydroxy-8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)éthyl]phosphonique ou un sel pharmaceutiquement acceptable de celui-ci;
 l'acide [2-(4,4-diméthyl-8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)éthyl]phosphonique ou un sel pharmaceutiquement acceptable de celui-ci;
 l'acide 2-[3-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)propyl]phosphonique ou un sel pharmaceutiquement acceptable de celui-ci;
 l'acide 8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-ène-2-acétique ou un sel pharmaceutiquement acceptable de celui-ci;
 l'acide 3-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)propanoïque ou un sel pharmaceutiquement acceptable de celui-ci;
 la 2-[(1H-tétrazol-5-yl)méthyl]-2,6-diazabicyclo[5,2,0]non-1(7)-ène-8,9-dione ou un sel pharmaceutiquement acceptable de celle-ci, ou
 l'acide 2-(9,10-dioxo-2,7-diazabicyclo[6,2,0]déc-1(8)-èn-2-yl)éthyl]phosphonique ou un sel pharmaceutiquement acceptable de celui-ci.

7. Composé suivant l'une quelconque des revendications 1 à 6, sous la forme d'un sel de métal alcalin, de métal alcalino-terreux ou d'ammonium.

8. Procédé de préparation d'un composé de formule (I) tel que défini dans la revendication 1, qui comprend :
- a) la réaction d'un composé de formule (II) :



(II)

où :

R¹ est tel que défini à la revendication 1 et OR¹² représente tout radical alcoxy ou aralcoxy partant, avec un composé de formule (III) :



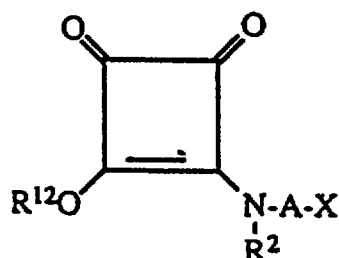
où :

R², A et X sont tels que définis à la revendication 1, ou un sel ou une forme protégée de celui-ci, si nécessaire l'élimination de tout radical protecteur, pour donner un composé de formule (I),



dans lequel R^2 est tel que défini à la revendication 1, si désiré isolé sous forme d'un sel pharmaceutiquement acceptable;

b) la réaction d'un composé de formule (IV) :



(IV)

où :

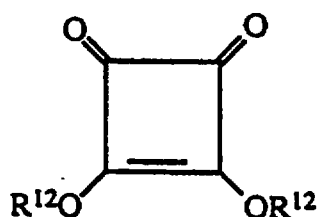
X , R^2 et R^{12} sont tels que définis ci-dessus ou d'un sel ou d'une forme protégée de celui-ci avec un composé de formule (V) :



où :

R^1 est tel que défini à la revendication 1, et élimination de tout groupe protecteur, pour donner un composé correspondant de formule (I) ou un sel de celui-ci;

c) la réaction d'un composé de formule (VI) :



(VI)

où :

les R^{12} sont tels que définis ci-dessus et sont chacun identiques ou différents, avec un composé de formule (VII) :

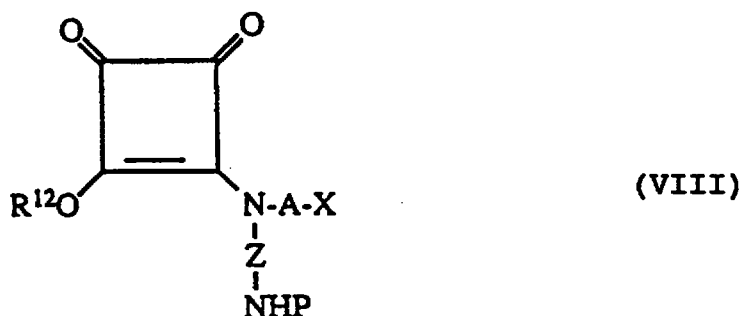


où :

X est tel que défini à la revendication 1, ou un sel ou une forme protégée de celui-ci, Z et A sont tels que définis à la revendication 1, si nécessaire l'élimination de tout groupe protecteur, pour donner un composé correspondant ayant la formule (I), dans lequel R^1 et R^2 , pris ensemble, sont Z ; A et X sont tels que définis ci-dessus;



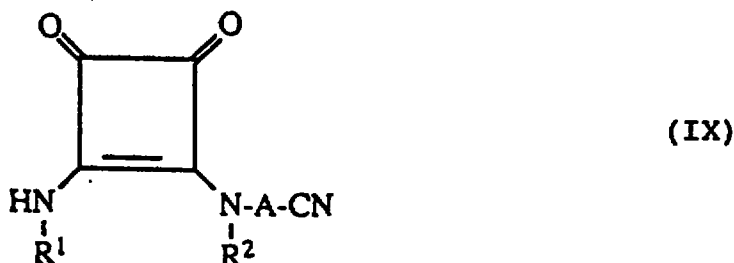
d) la déprotection, sélectivement si nécessaire, et la cyclisation d'un composé de formule (VIII) :



où :

X, Z, R¹² et A sont tels que définis ci-dessus ou un sel ou une forme protégée de celui-ci et P est un groupe protecteur d'amino, qui est de préférence éliminable sélectivement si X est protégé, pour donner un composé correspondant ayant la formule (I), où R¹ et R² sont Z, si nécessaire aussi l'élimination de tout groupe protecteur sur X;

e) la réaction d'un composé de formule (IX) :



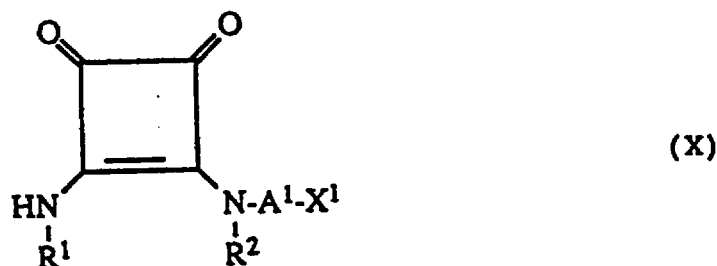
où :

R¹, R² et A sont tels que définis à la revendication 1, avec un azoture, pour donner un composé correspondant de formule (I) où X est 5-tétrazolye;

f) la conversion d'un composé de formule (I) dans lequel R³, R⁴ et R⁵ sont des radicaux alcoyle pour donner un composé de formule (I) dans lequel R³, R⁴ et R⁵ sont hydrogène ou un sel de celui-ci;

g) l'acidification d'un sel d'un composé de formule (I) pour donner l'acide libre ou la basification d'un acide de formule (I) pour donner un sel de celui-ci, ou

h) la thermolyse d'un composé de formule (X) :



où :

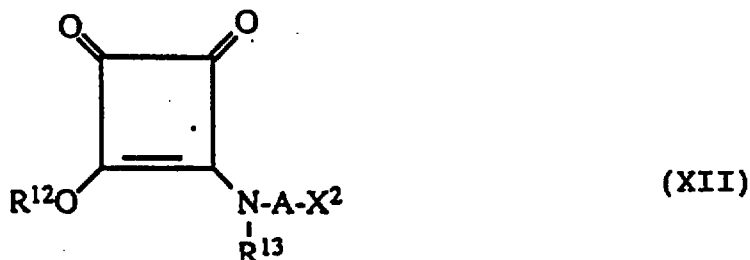
R¹ est défini ci-dessus, X¹ est -CO₂R³ ou -P(O)(OR⁴)(OR⁵), où R³, R⁴ et R⁵ sont tous alcoyle, 3,5-dioxo-1,2,4-oxadiazolidin-2-yle ou 5-tétrazolye protégé et A¹ représente alcoylène de 2 à 6 atomes de carbone substitués par un radical -S(O)_m-aryle où m représente 1 ou 2, si nécessaire l'élimination de tout groupe protecteur pour donner un composé correspondant de formule (I) dans



lequel A est alcénylène de 2 à 6 atomes de carbone.

9. Composition pharmaceutique comprenant un composé de formule (I) ou un sel pharmaceutiquement acceptable de celui-ci, suivant l'une quelconque des revendications 1 à 7, et d'un support pharmaceutiquement acceptable.

10. Composé de formule générale (XII) :



ou un sel de celui-ci,
où :

X² représente -CN, -COOR¹⁴ où R¹⁴ est hydrogène, alcoyle en 1 à 6 atomes de carbone ou un radical protecteur de carboxyle, -P(O)(OR¹⁵)(OR¹⁶) où R¹⁵ et R¹⁶ sont hydrogène ou alcoyle en 1 à 6 atomes de carbone, 3,5-dioxo-1,2,4-oxadiazolidinyle ou 5-tétrazolyle facultativement protégé, R¹² représente un groupe alcoxy ou aralcoxy partant et R¹³ représente hydrogène, alcoyle en 1 à 6 atomes de carbone, alcényle en 2 à 6 atomes de carbone, phénylcoyle en 7 à 12 atomes de carbone ou NHP où P est un radical protecteur d' amino et A et Z sont tels que définis dans la revendication 1.

11. Composé suivant la revendication 10, dans lequel R¹³ est hydrogène, méthyle, alcoyle, méthallyle ou benzyle.

12. Composé suivant la revendication 10, dans lequel P est benzyloxycarbonyl ou un dérivé substitué de celui-ci.

13. Composé suivant l'une quelconque des revendications 10 à 12, dans lequel R¹² est méthyle ou éthyle.

14. Composé suivant l'une quelconque des revendications 11 à 13, dans lequel R¹⁴, R¹⁵ et R¹⁶ sont choisis parmi méthyle et éthyle.

15. Composé suivant la revendication 11, qui est l'un des suivants :

l'ester diéthylique de l'acide [2-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]éthyl]phosphonique;
l'ester diéthylique de l'acide [2-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]méthyl]phosphonique;
l'ester diéthylique de l'acide [3-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]phosphonique;
l'ester diéthylique de l'acide [4-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]butyl]phosphonique;
l'ester diéthylique de l'acide [(E)-4-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]-2-butèn-1-yl]-

phosphonique;

l'ester diéthylique de l'acide [2-[2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)méthylamino]éthyl]-phosphonique;

l'ester diéthylique de l'acide [[2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)méthylamino]méthyl]-phosphonique;

l'ester phénylméthylque de l'acide [3-[[2-(diéthoxyphosphinyl)éthyl]-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]carbamique;

l'ester 1,1-diméthyléthylque de l'acide [3-[[2-(diéthoxyphosphinyl)éthyl]-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]-2-hydroxypropyl]carbamique;

l'ester phénylméthylque de l'acide [3-[[1,1-diméthyléthoxyphosphinyl]méthyl]-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]carbamique;

l'ester 1,1-diméthyléthylque de l'acide [3-[(cyanométhyl)-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]carbamique, ou

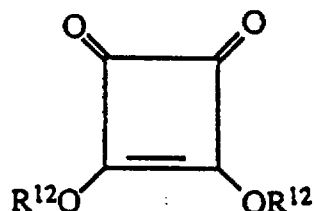
l'ester 1,1-diméthyléthylque de l'acide [4-[[2-diéthoxyphosphinyl]éthyl]-(2-éthoxy-3,4-dioxo-1-cyclo-



butèn-1-yl)amino]butyl]carbamique.

16. Procédé de préparation d'un composé de formule (XII) tel que montré et défini dans la revendication 11, qui comprend :

a) la réaction d'un composé de formule (VI) :



(VI)

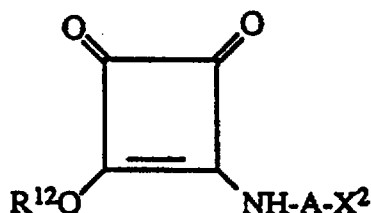
avec un composé de formule :

$\text{HR}^{13}\text{N-A-X}^2$ (XIII)

où :

A, R^{12} , R^{13} et X^2 sont tels que définis dans la revendication 11, pour donner un composé correspondant de formule (XII), ou

b) la N-alcoylation d'un composé de formule (XIV) :



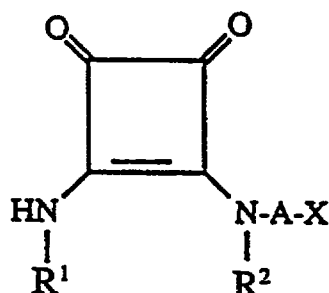
(XIV)

où :

R^{12} , A et X^2 sont tels que définis ci-dessus, en présence d'une base forte, avec un composé de formule $\text{R}^2\text{-halo}$ où halo est un halogène et R^2 est tel que défini ci-dessus sauf hydrogène, pour donner un composé correspondant de formule (XII).

Revendications pour l'Etat contractant suivant : ES

1. Procédé de préparation d'un composé de formule :



(I)

où :

R^1 est hydrogène, alcoyle en 1 à 6 atomes de carbone ou phénylcoyle en 7 à 12 atomes de carbone;

R^2 est hydrogène, alcoyle en 1 à 6 atomes de carbone, alcényle en 2 à 6 atomes de carbone ou



phénylalcyle en 7 à 12 atomes de carbone, ou

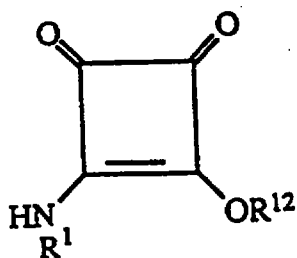
R¹ et R², pris ensemble, sont Z, qui est -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- ou -CH₂C(R⁸)(R⁹)-C(R¹⁰)-(R¹¹)CH₂-, où R⁶, R⁸ et R¹⁰ sont, indépendamment, hydrogène, alcyle en 1 à 6 atomes de carbone ou hydroxyle, et R⁷, R⁹ et R¹¹ sont, indépendamment, hydrogène ou alcyle en 1 à 6 atomes de carbone;

A est alcylène en 1 à 6 atomes de carbone ou alcénylène en 2 à 6 atomes de carbone;

X est -CO₂R³ dans lequel R³ est hydrogène ou alcyle en 1 à 6 atomes de carbone, -P(O)(OR⁴)-(OR⁵) dans lequel R⁴ et R⁵ sont, indépendamment, hydrogène ou alcyle en 1 à 6 atomes de carbone, 3,5-dioxo-1,2,4-oxadiazolidin-2-yle ou 5-tétrazolyle, ou

un sel pharmaceutiquement acceptable de celui-ci, qui comprend l'une des réactions suivantes :

a) la réaction d'un composé de formule (II) :



(II)

où :

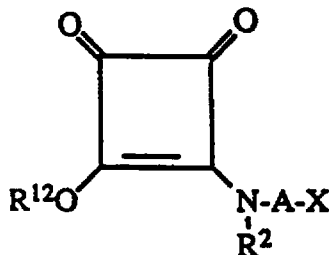
R¹ est tel que défini ci-dessus et OR¹² représente tout radical alcoxy ou aralcoxy partant avec un composé de formule (III) :

HNR²-A-X (III)

où :

R², A et X sont tels que définis ci-dessus ou un sel ou une forme protégée de celui-ci, si nécessaire l'élimination de tout radical protecteur, pour donner un composé de formule (I), dans lequel R² est tel que défini ci-dessus, si désiré isolé sous forme d'un sel pharmaceutiquement acceptable;

b) la réaction d'un composé de formule (IV) :



(IV)

où :

X, R² et R¹² sont tels que définis ci-dessus ou d'un sel ou d'une forme protégée de celui-ci avec un composé de formule (V) :

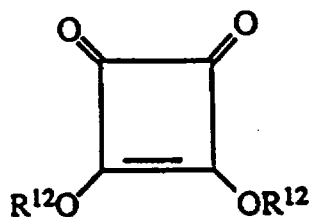
H₂NR¹ (V)

où :

R¹ est tel que défini ci-dessus et l'élimination de tout groupe protecteur, pour donner un composé correspondant de formule (I) ou un sel de celui-ci;



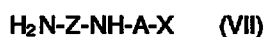
c) la réaction d'un composé de formule (VI) :



(VI)

où :

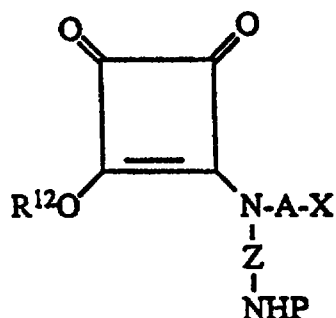
les R^{12} sont tels que définis ci-dessus et sont chacun identiques ou différents, avec un composé de formule (VII) :



où :

X est tel que défini ci-dessus ou un sel ou une forme protégée de celui-ci, Z et A sont tels que définis ci-dessus, si nécessaire l'élimination de tout groupe protecteur, pour donner un composé correspondant ayant la formule (I), dans lequel R^1 et R^2 , pris ensemble, sont Z; A et X sont tels que définis ci-dessus;

d) la déprotection, sélectivement si nécessaire, et la cyclisation d'un composé de formule (VIII) :

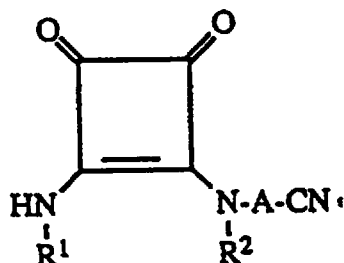


(VIII)

où :

X, Z, R^{12} et A sont tels que définis ci-dessus ou un sel ou une forme protégée de celui-ci et P est un groupe protecteur d'amino, qui est de préférence éliminable sélectivement si X est protégé, pour donner un composé correspondant ayant la formule (I), où R^1 et R^2 sont Z, si nécessaire aussi l'élimination de tout groupe protecteur sur X;

e) la réaction d'un composé de formule (IX) :



(IX)

où :

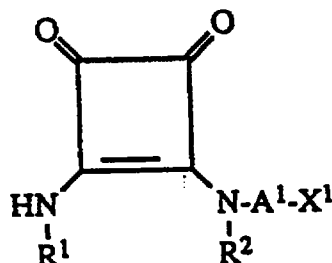
R^1 , R^2 et A sont tels que définis ci-dessus, avec un azoture, pour donner un composé correspondant de formule (I) où X est 5-tétrazole;



f) la conversion d'un composé de formule (I) dans lequel R^3 , R^4 et R^5 sont des radicaux alcoyle pour donner un composé de formule (I) dans lesquels R^3 , R^4 et R^5 sont hydrogène ou un sel de celui-ci;

g) l'acidification d'un sel d'un composé de formule (I) pour donner l'acide libre ou la basification d'un acide de formule (I) pour donner un sel de celui-ci, ou

h) la thermolyse d'un composé de formule (X) :



(X)

où :

R^1 est défini ci-dessus, X^1 est $-CO_2R^3$ ou $-P(O)(OR^4)(OR^5)$, où R^3 , R^4 et R^5 sont tous alcoyle, 3,5-dioxo-1,2,4-oxadiazolidin-2-yle ou 5-tétrazolyle protégé et A^1 représente alcoylène de 2 à 6 atomes de carbone substitués par un radical $-S(O)_m$ -aryle où m représente 1 ou 2, si nécessaire l'élimination de tout groupe protecteur pour donner un composé correspondant de formule (I) dans lequel A est alcénylène de 2 à 6 atomes de carbone.

2. Procédé suivant la revendication 1, dans lequel R^1 et R^2 sont, indépendamment, hydrogène, méthyle, allyle, méthallyle ou benzyle ou, R^1 et R^2 , pris ensemble, sont $-CH_2CH_2-$, $-CH_2C(R^6)(R^7)CH_2-$ ou $-CH_2C(R^8)(R^9)-C(R^{10})(R^{11})CH_2-$, où R^6 , R^8 et R^{10} sont, indépendamment, hydrogène, alcoyle en 1 à 6 atomes de carbone ou hydroxyle, et R^7 , R^9 et R^{11} sont, indépendamment, hydrogène ou alcoyle en 1 à 6 atomes de carbone.

3. Procédé suivant la revendication 1 ou 2, dans lequel A est un alcoylène en 1 à 4 atomes de carbone ou trans-2-buténylène.

4. Procédé suivant l'une quelconque des revendications 1 à 3, dans lequel X est carboxyle, phosphonyle ou 5-tétrazolyle.

5. Procédé suivant la revendication 1, dans lequel le produit est :

la N-(2-amino-3,4-dioxo-1-cyclobutène-1-yl)bêta-alanine;

l'ester éthylique de la N-(2-amino-3,4-dioxo-1-cyclobutène-1-yl)glycine;

la 2-[2-[(2-amino-3,4-dioxo-1-cyclobutène-1-yl)amino]éthyl]-1,2,4-oxadiazolidine-3,5-dione;

la N-[2-(méthylamino)-3,4-dioxo-1-cyclobutène-1-yl)bêta-alanine;

la N-(2-amino-3,4-dioxo-1-cyclobutène-1-yl)-N-(2-propényl)glycine;

la N-(2-amino-3,4-dioxo-1-cyclobutène-1-yl)-N-(2-méthyl-2-propényl)glycine;

l'acide [2-[(2-amino-3,4-dioxo-1-cyclobutène-1-yl)amino]éthyl]phosphonique;

l'acide [[2-(2-amino-3,4-dioxo-1-cyclobutène-1-yl)amino]méthyl]phosphonique;

l'acide [3-[(2-amino-3,4-dioxo-1-cyclobutène-1-yl)amino]propyl]phosphonique;

l'acide [4-[(2-amino-3,4-dioxo-1-cyclobutène-1-yl)amino]butyl]phosphonique;

l'acide [(E)-4-[(2-amino-3,4-dioxo-1-cyclobutène-1-yl)amino]-2-butényl]phosphonique;

l'acide [2-[(2-amino-3,4-dioxo-1-cyclobutène-1-yl)méthylamino]éthyl]phosphonique;

l'acide [[2-(2-amino-3,4-dioxo-1-cyclobutène-1-yl)méthylamino]méthyl]phosphonique;

l'acide [2-(7,8-dioxo-2,5-diazabicyclo[4,2,0]oct-1(6)-ène-2-yl)éthyl]phosphonique;

l'acide [2-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-ène-2-yl)éthyl]phosphonique;

l'acide [2-(4-hydroxy-8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-ène-2-yl)éthyl]phosphonique;

l'acide [2-(4,4-diméthyl-8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-ène-2-yl)éthyl]phosphonique;

l'acide [3-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-ène-2-yl)propyl]phosphonique;

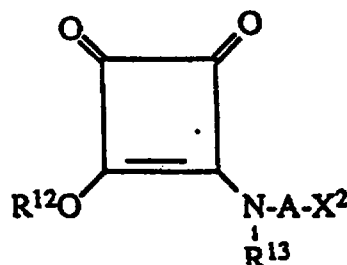
l'acide [(E)-3-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-ène-2-yl)-1-propényl]phosphonique;

l'acide 8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-ène-2-acétique;



l'acide 3-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)propanoïque;
 la 2-[(1H-tétrazol-5-yl)méthyl]-2,6-diazabicyclo[5,2,0]non-1(7)-ène-8,9-dione;
 la 2-[2-(1H-tétrazol-5-yl)éthyl]-2,6-diazabicyclo[5,2,0]non-1(7)-ène-8,9-dione;
 la N-(2-amino-3,4-dioxo-1-cyclobutényl)glycine;
 l'acide 4-[2-amino-3,4-dioxo-1-cyclobutényl]amino]butanoïque;
 l'acide 3-[[3,4-dioxo-2-[(phénylméthyl)amino]-1-cyclobutényl]amino]propanoïque;
 la N-(2-amino-3,4-dioxo-1-cyclobutényl)-N-(phénylméthyl)glycine, ou
 l'acide [2-(9,10-dioxo-2,7-diazabicyclo[6,2,0]déc-1(8)-èn-2-yl)éthyl]phosphonique, ou un sel pharmaceutiquement acceptable de ceux-ci.

6. Procédé suivant l'une quelconque des revendications 1 à 5, dans lequel le produit est obtenu sous la forme d'un sel de métal alcalin, de métal alcalinoterreux ou d'ammonium.
7. Procédé de préparation d'une composition pharmaceutique, qui comprend la conversion d'un composé de formule (I) ou d'un sel pharmaceutiquement acceptable de celui-ci tel que défini dans l'une quelconque des revendications 1 à 6 et d'un support pharmaceutiquement acceptable, en une forme appropriée pour une administration thérapeutique.
8. Procédé de préparation d'un composé de formule générale (XII) :

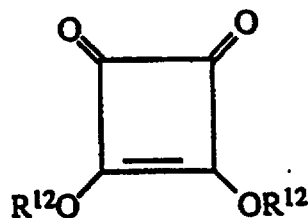


(XII)

ou d'un sel de celui-ci,
 où :

X² représente -CN, -COOR¹⁴ où R¹⁴ est hydrogène, alcoyle en 1 à 6 atomes de carbone ou un radical protecteur de carboxyle, -P(O)(OR¹⁵)(OR¹⁶) où R¹⁵ et R¹⁶ sont hydrogène ou alcoyle en 1 à 6 atomes de carbone, 3,5-dioxo-1,2,4-oxadiazolidinyle ou 5-tétrazolyle facultativement protégé; R¹² représente un groupe alcoxy ou aralcoxy partant et R¹³ représente hydrogène, alcoyle en 1 à 6 atomes de carbone, alcényle en 2 à 6 atomes de carbone, phénylcoyle en 7 à 12 atomes de carbone ou NHP où P est un radical protecteur d' amino et A est alcoylène de 1 à 6 atomes de carbone ou alcénylène de 2 à 6 atomes de carbone, Z est tel que défini dans la revendication 1, qui comprend :

- a) la réaction d'un composé de formule (VI) :



(VI)

avec un composé de formule :

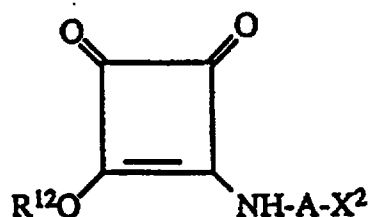


où :

A, R¹², R¹³ et X² sont tels que définis ci-dessus, pour donner un composé correspondant de formule (XII), ou



b) la N-alcoylation d'un composé de formule (XIV) :

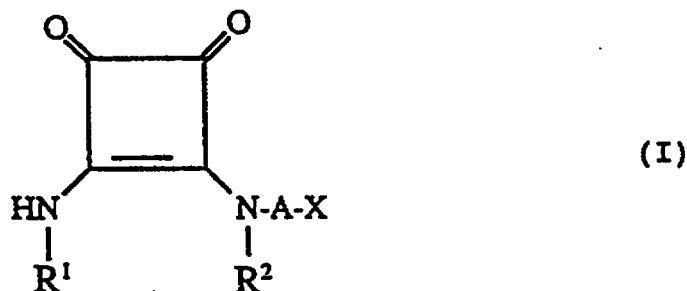


(XIV)

où :

R¹², A et X² sont tels que définis ci-dessus, en présence d'une base forte, avec un composé de formule R²-halo, où halo est un halogène et R² est tel que défini ci-dessus, sauf hydrogène, pour donner un composé correspondant de formule (XII).

9. Procédé suivant la revendication 8, dans lequel R¹³ est hydrogène, méthyle, alcoyle, méthallyle ou benzyle.
10. Procédé suivant la revendication 8, dans lequel P est benzyloxycarbonyle ou un dérivé substitué de celui-ci.
11. Procédé suivant l'une quelconque des revendications 8 à 10, dans lequel R¹² est méthyle ou éthyle.
12. Procédé suivant l'une quelconque des revendications 9 à 12, dans lequel R¹⁴, R¹⁵ et R¹⁶ sont choisis parmi méthyle et éthyle.
13. Procédé suivant la revendication 9, dans lequel le produit est l'un des suivants :
 - l'ester diéthylique de l'acide [2-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]éthyl]phosphonique;
 - l'ester diéthylique de l'acide [[2-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]méthyl]phosphonique;
 - l'ester diéthylique de l'acide [3-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]phosphonique;
 - l'ester diéthylique de l'acide [4-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]butyl]phosphonique;
 - l'ester diéthylique de l'acide [(E)-4-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]-2-butèn-1-yl]phosphonique;
 - l'ester diéthylique de l'acide [2-[2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)méthylamino]éthyl]phosphonique;
 - l'ester diéthylique de l'acide [[2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)méthylamino]méthyl]phosphonique;
 - l'ester phénylméthylque de l'acide [3-[[2-(diéthoxyphosphinyl)éthyl]-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]carbamique;
 - l'ester 1,1-diméthyléthylque de l'acide [3-[[2-(diéthoxyphosphinyl)éthyl]-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]-2-hydroxypropyl]carbamique;
 - l'ester phénylméthylque de l'acide [3-[[1,1-diméthyléthylloxycarbonyl)méthyl]-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]carbamique;
 - l'ester 1,1-diméthyléthylque de l'acide [3-[(cyanométhyl)-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]carbamique, ou
 - l'ester 1,1-diméthyléthylque de l'acide [4-[[2-(diéthoxyphosphinyl)éthyl]-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]butyl]carbamique.


Revendications pour l'Etat contractant suivant : GR
1. Procédé de préparation d'un composé de formule :


15 où :

R¹ est hydrogène, alcoyle en 1 à 6 atomes de carbone ou phénylcoyle en 7 à 12 atomes de carbone;

R² est hydrogène, alcoyle en 1 à 6 atomes de carbone, alcényle en 2 à 6 atomes de carbone ou phénylcoyle en 7 à 12 atomes de carbone, ou

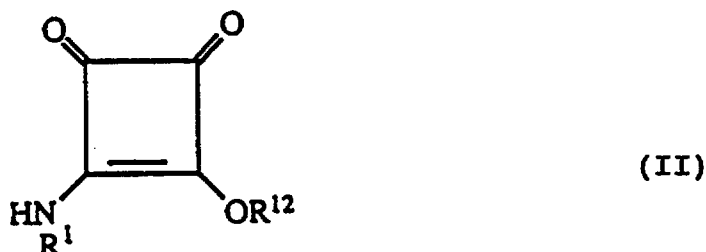
R¹ et R², pris ensemble, sont Z, qui est -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- ou -CH₂C(R⁸)(R⁹)-C(R¹⁰)-(R¹¹)CH₂-, où R⁶, R⁸ et R¹⁰ sont, indépendamment, hydrogène, alcoyle en 1 à 6 atomes de carbone ou hydroxyle, et R⁷, R⁹ et R¹¹ sont, indépendamment, hydrogène ou alcoyle en 1 à 6 atomes de carbone;

A est alcoylène en 1 à 6 atomes de carbone ou alcénylène en 2 à 6 atomes de carbone;

X est -CO₂R³ dans lequel R³ est hydrogène ou alcoyle en 1 à 6 atomes de carbone, -P(O)(OR⁴)-(OR⁵) dans lequel R⁴ et R⁵ sont, indépendamment, hydrogène ou alcoyle en 1 à 6 atomes de carbone, 3,5-dioxo-1,2,4-oxadiazolidin-2-yle ou 5-tétrazolye, ou

un sel pharmaceutiquement acceptable de celui-ci, qui comprend l'une des réactions suivantes :

a) la réaction d'un composé de formule (II) :



40 où :

R¹ est tel que défini ci-dessus et OR¹² représente tout radical alcoxy ou aralcoxy partant avec un composé de formule (III) :

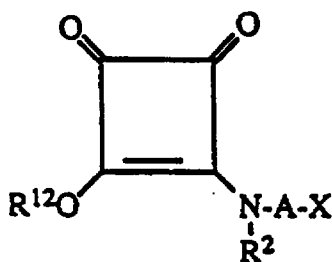
45 HNR²-A-X (III)

où :

R², A et X sont tels que définis ci-dessus ou un sel ou une forme protégée de celui-ci, si nécessaire l'élimination de tout radical protecteur pour donner un composé de formule (I), dans lequel R² est tel que défini ci-dessus, si désiré isolé sous forme d'un sel pharmaceutiquement acceptable;



b) la réaction d'un composé de formule (IV) :



(IV)

où :

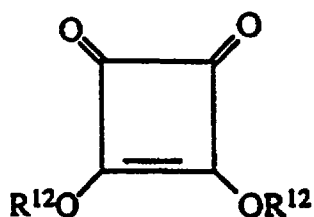
X, R² et R¹² sont tels que définis ci-dessus ou d'un sel ou d'une forme protégée de celui-ci avec un composé de formule (V) :



où :

R¹ est tel que défini ci-dessus et l'élimination de tout groupe protecteur pour donner un composé correspondant de formule (I) ou un sel de celui-ci, ou

c) la réaction d'un composé de formule (VI) :



(VI)

où :

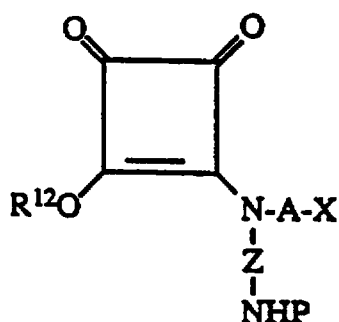
les R¹² sont tels que définis ci-dessus et sont chacun identiques ou différents, avec un composé de formule (VII) :



où :

X est tel que défini ci-dessus ou un sel ou une forme protégée de celui-ci, Z et A sont tels que définis ci-dessus, si nécessaire l'élimination de tout groupe protecteur, pour donner un composé correspondant ayant la formule (I), dans lequel R¹ et R² pris ensemble sont Z; A est X sont tels que définis ci-dessus;

d) la déprotection, sélectivement si nécessaire, et la cyclisation d'un composé de formule (VIII) :



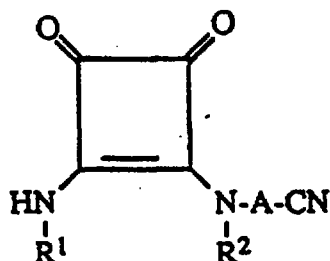
(VIII)



où :

X, Z, R¹² et A sont tels que définis ci-dessus ou un sel ou une forme protégée de celui-ci et P est un groupe protecteur d'amino, qui est de préférence éliminable sélectivement si X est protégé, pour donner un composé correspondant ayant la formule (I), où R¹ et R² sont Z, si nécessaire aussi l'élimination de tout groupe protecteur sur X;

e) la réaction d'un composé de formule (IX) :



(IX)

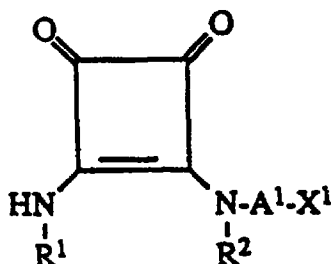
où :

R¹ R² et A sont tels que définis ci-dessus, avec un azoture, pour donner un composé correspondant de formule (I) où X est 5-tétrazolye;

f) la conversion d'un composé de formule (I) dans lequel R³, R⁴ et R⁵ sont des radicaux alcoyle pour donner un composé de formule (I) dans lequel R³, R⁴ et R⁵ sont hydrogène ou un sel de celui-ci;

g) l'acidification d'un sel d'un composé de formule (I) pour donner l'acide libre ou la basification d'un acide de formule (I) pour donner un sel de celui-ci, ou

h) la thermolyse d'un composé de formule (X) :



(X)

où :

R¹ est défini ci-dessus, X¹ est -CO₂R³ ou -P(O)(OR⁴)(OR⁵), où R³, R⁴ et R⁵ sont tous alcoyle, 3,5-dioxo-1,2,4-oxadiazolidin-2-yle ou 5-tétrazolye protégé et A¹ représente alcoylène de 2 à 6 atomes de carbone substitués par un radical -S(O)_m-aryle où m représente 1 ou 2, si nécessaire l'élimination de tout groupe protecteur pour donner un composé correspondant de formule (I) dans lequel A est alcénylène de 2 à 6 atomes de carbone.

2. Procédé suivant la revendication 1, dans lequel R¹ et R² sont, indépendamment, hydrogène, méthyle, allyle, méthallyle ou benzyle ou R¹ et R², pris ensemble, sont -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- ou -CH₂C(R⁸)(R⁹)-C(R¹⁰)(R¹¹)CH₂-, où R⁶, R⁸ et R¹⁰ sont, indépendamment, hydrogène, alcoyle en 1 à 6 atomes de carbone ou hydroxyle, et R⁷, R⁹ et R¹¹ sont, indépendamment, hydrogène ou alcoyle en 1 à 6 atomes de carbone.
3. Procédé suivant la revendication 1 ou 2, dans lequel A est un alcoylène en 1 à 4 atomes de carbone ou trans-2-buténylène.
4. Procédé suivant l'une quelconque des revendications 1 à 3, dans lequel X est carboxyle, phosphonyle ou 5-tétrazolye.



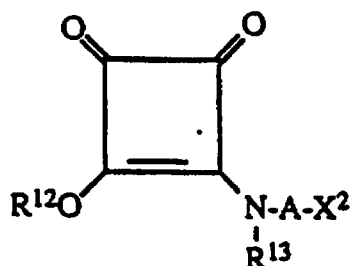
5. Procédé suivant la revendication 1, dans lequel le produit est :

- la N-(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)bêta-alanine;
- l'ester éthylique de la N-(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)glycine;
- la 2-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]éthyl]-1,2,4-oxadiazolidine-3,5-dione;
- la N-(2-(méthylamino)-3,4-dioxo-1-cyclobutèn-1-yl)bêta-alanine;
- la N-(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)-N-(2-propèn-1-yl)glycine;
- la N-(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)-N-(2-méthyl-2-propèn-1-yl)glycine;
- l'acide [2-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]éthyl]phosphonique;
- l'acide [[[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]méthyl]phosphonique];
- l'acide [3-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]phosphonique;
- l'acide [4-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]butyl]phosphonique;
- l'acide [(E)-4-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]-2-butèn-1-yl]phosphonique;
- l'acide [2-[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)méthylamino]éthyl]phosphonique;
- l'acide [[[(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)méthylamino]méthyl]phosphonique];
- l'acide [2-(7,8-dioxo-2,5-diazabicyclo[4,2,0]oct-1(6)-èn-2-yl)éthyl]phosphonique;
- l'acide [2-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)éthyl]phosphonique;
- l'acide [2-(4-hydroxy-8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)éthyl]phosphonique;
- l'acide [2-(4,4-diméthyl-8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)éthyl]phosphonique;
- l'acide [3-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)propyl]phosphonique;
- l'acide [(E)-3-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)-1-propèn-1-yl]phosphonique;
- l'acide 8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-ène-2-acétique;
- l'acide 3-(8,9-dioxo-2,6-diazabicyclo[5,2,0]non-1(7)-èn-2-yl)propanoïque;
- la 2-[(1H-tétrazol-5-yl)méthyl]-2,6-diazabicyclo[5,2,0]non-1(7)-ène-8,9-dione;
- la 2-[2-(1H-tétrazol-5-yl)éthyl]-2,6-diazabicyclo[5,2,0]non-1(7)-ène-8,9-dione;
- la N-(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)glycine;
- l'acide 4-[2-amino-3,4-dioxo-1-cyclobutèn-1-yl)amino]butanoïque;
- l'acide 3-[[3,4-dioxo-2-[(phénylméthyl)amino]-1-cyclobutèn-1-yl)amino]propanoïque;
- la N-(2-amino-3,4-dioxo-1-cyclobutèn-1-yl)-N-(phénylméthyl)glycine, ou
- l'acide [2-(9,10-dioxo-2,7-diazabicyclo[6,2,0]déc-1(8)-èn-2-yl)éthyl]phosphonique, ou un sel pharmaceutiquement acceptable de ceux-ci.

6. Procédé suivant l'une quelconque des revendications 1 à 5, dans lequel le produit est obtenu sous la forme d'un sel de métal alcalin, de métal alcalinoterreux ou d'ammonium.

7. Procédé de préparation d'une composition pharmaceutique, qui comprend la conversion d'un composé de formule (I) ou d'un sel pharmaceutiquement acceptable de celui-ci tel que défini dans l'une quelconque des revendications 1 à 6 et d'un support pharmaceutiquement acceptable, en une forme appropriée pour une administration thérapeutique.

8. Composé de formule générale (XII) :



(XII)

ou un sel de celui-ci,

où :

X² représente -CN, -COOR¹⁴ où R¹⁴ est hydrogène, alcoyle en 1 à 6 atomes de carbone ou un radical protecteur de carboxyle, -P(O)(OR¹⁵)(OR¹⁶) où R¹⁵ et R¹⁶ sont hydrogène ou alcoyle en 1 à 6 atomes de carbone, 3,5-dioxo-1,2,4-oxadiazolidinyle ou 5-tétrazolyle facultativement protégé, R¹² représente un groupe alcoxy ou aralcoxy partant et R¹³ représente hydrogène, alcoyle en 1 à 6 atomes de carbone, alcényle en 2 à 6 atomes de carbone, phénylcoyle en 7 à 12 atomes de carbone ou NHP



où P est un radical protecteur d'amino et A est alcoylène en 1 à 6 atomes de carbone ou alcénylène en 2 à 6 atomes de carbone et Z est tel que défini dans la revendication 1.

- 5 9. Composé suivant la revendication 8, dans lequel R¹³ est hydrogène, méthyle, alcoyle, méthallyle ou benzyle.
10. Composé suivant la revendication 8, dans lequel P est benzyloxycarbonyl ou un dérivé substitué de celui-ci.
- 10 11. Composé suivant l'une quelconque des revendications 8 à 10, dans lequel R¹² est méthyle ou éthyle.
12. Composé suivant l'une quelconque des revendications 9 à 11, dans lequel R¹⁴, R¹⁵ et R¹⁶ sont choisis parmi méthyle et éthyle.
- 15 13. Composé suivant la revendication 9, qui est l'un des suivants :
 - l'ester diéthylique de l'acide [2-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]éthyl]phosphonique;
 - l'ester diéthylique de l'acide [[2-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]méthyl]phosphonique;
 - l'ester diéthylique de l'acide [3-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]phosphonique;
 - l'ester diéthylique de l'acide [4-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]butyl]phosphonique;
 - 20 l'ester diéthylique de l'acide [(E)-4-[(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]-2-butène]-phosphonique;
 - l'ester diéthylique de l'acide [2-[2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)méthylamino]éthyl]-phosphonique;
 - l'ester diéthylique de l'acide [[2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)méthylamino]méthyl]-phosphonique;
 - 25 l'ester phénylméthylrique de l'acide [3-[[2-(diéthoxyphosphinyl)éthyl]-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]carbamique;
 - l'ester 1,1-diméthyléthylrique de l'acide [3-[[2-(diéthoxyphosphinyl)éthyl]-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]-2-hydroxypropyl]carbamique;
 - 30 l'ester phénylméthylrique de l'acide [3-[[1,1-diméthyléthylloxycarbonyl)méthyl]-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]carbamique;
 - l'ester 1,1-diméthyléthylrique de l'acide [3-[(cyanométhyl)-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]propyl]carbamique, ou
 - l'ester 1,1-diméthyléthylrique de l'acide [4-[[2-diéthoxyphosphinyl)éthyl]-(2-éthoxy-3,4-dioxo-1-cyclobutèn-1-yl)amino]butyl]carbamique.
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