

The title of the invention is:

Novel phospholipid derivatives

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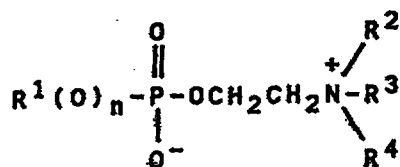
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Novel phospholipid derivatives

European patent application 108 565 relates to compounds of the general formula

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and their pharmaceutically utilizable salts, in which R^1 is an aliphatic hydrocarbon radical having 8 - 30 C atoms and the radicals R^2 , R^3 and R^4 are identical or different and
15 are hydrogen or lower alkyl radicals, or in which the group $\text{NR}^2\text{R}^3\text{R}^4$ is a cyclic ammonium group, and n has the value 0 or 1. An antitumoural action and an antifungal action are indicated for these compounds.

20 The invention relates to alkyl or alkene phosphates in which the choline radical is part of a heterocyclic ring, to a process for the preparation of the class of compounds, to the drugs containing the compounds as active ingredients and to processes for the preparation of said drugs.

25

Surprisingly, the compounds according to the invention possess a better antitumoural action than the open-chain derivatives described in EP-A 108 565.

30 The invention further relates to processes for the preparation and processes for the purification of the novel compounds.

The first step of the process consists in reacting
35 phosphorus oxychloride with the long-chain alcohol in halogenated or aromatic hydrocarbons, saturated cyclic ethers or acyclic ethers.

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The first step of process A consists in reacting phosphorus oxychloride with long-chain alcohol in halogenated hydrocarbons, saturated cyclic ethers, acyclic ethers, saturated hydrocarbons having 5 to 10 C atoms or liquid aromatic hydrocarbons which can also be substituted by halogen (especially chlorine), or in mixtures of the above-mentioned solvents, or without a solvent, optionally in the presence of a basic substance conventionally used for this purpose.

10

Examples of possible halogenated hydrocarbons are hydrocarbons having 1 to 6 C atoms, one or more or all of the hydrogen atoms being replaced with chlorine atoms. Methylene chloride, chloroform, ethylene chloride, chlorobenzene and dichlorobenzene, for example, can be used. In the case of halogen-substituted aromatic hydrocarbons, these are preferably substituted by one or two halogen atoms.

20 Examples of saturated cyclic ethers which can be used are ethers with a ring size of 5-6 which consist of carbon atoms and one or 2 oxygen atoms, examples of such ethers being tetrahydrofuran and dioxane.

25 The acyclic ethers consist of 2 to 8 carbon atoms and are liquid, possible examples being diethyl ether, diisobutyl ether, methyl tert-butyl ether and diisopropyl ether.

Possible saturated hydrocarbons are unbranched and branched hydrocarbons which consist of 5 to 10 carbon atoms and are liquid, possible examples being pentane, hexane, heptane and cyclohexane.

35 Examples of possible aromatic hydrocarbons are benzene and alkyl-substituted benzenes, the alkyl substituents consisting of 1 to 5 carbon atoms.

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Possible basic substances both for the reaction of the phosphorus oxychloride with the long-chain alcohol and for the subsequent conversion to the phosphoric acid diester are amines, for example aliphatic amines of the formula
5 $NR_1R_2R_3$, R_1 , R_2 and R_3 being identical or different and being hydrogen or C_1 - C_6 - alkyl, or else aromatic amines such as pyridine, picoline and quinoline. The basic substance required for the conversion to the phosphoric acid diester can be added simultaneously with or else before the amino
10 alcohol or ammonio alcohol salt.

A solvent is necessary in every case for this reaction, i.e. if the first reaction step is carried out without a particular solvent, one must now be added. The molar ratio
15 of phosphorus oxychloride to the long-chain alcohol is for example between 1.5:1 and 0.8:1.

The amino alcohol or the ammonio alcohol salt is for example used in excess, based on the long-chain alcohol
20 (about 1.1 - 1.5 molar excess).

If the reaction of the phosphorus oxychloride with the long-chain alcohol is carried out in the presence of a basic substance, the amount of the basic substance is for
25 example 1 to 3 mol, based on 1 mol of $POCl_3$. The amount of basic substance used for the subsequent conversion to the phosphoric acid diester is for example 1 to 5 mol, based on 1 mol.

30 The temperature of the reaction of phosphorus oxychloride with the long-chain alcohol is between $-30^\circ C$ and $+30^\circ C$, preferably between $-15^\circ C$ and $+5^\circ C$ and especially between $-10^\circ C$ and $-5^\circ C$.

35 The duration of this reaction is for example 0.5 - 5 hours, preferably 1 - 3 hours and especially 1.5 - 2 hours. If it



is carried out in the presence of a basic substance, the reaction generally proceeds rapidly (about 30 minutes).

- The amino alcohol or the ammonio alcohol salt is then added in portions or all at once. Possible ammonio alcohol salts are those with mineral acids (for example sulphuric acid, hydrochloric acid) and also those with organic acids, for example acetic acid, paratoluenesulphonic acid and the like. This reaction step takes place in an inert solvent.
- Possible solvents here are the same ones as those used for the reaction of the phosphorus oxychloride with the long-chain alcohol, in the case where this reaction is carried out in a solvent.
- The basic substance is then added dropwise, either dissolved in one of the indicated solvents or without a solvent. The following are preferably used here as solvents for the basic substance: halogenated hydrocarbons, saturated cyclic ethers, acyclic ethers, saturated hydrocarbons having 5 to 10 carbon atoms, liquid aromatic hydrocarbons or mixtures of the above-mentioned solvents.

These are the same solvents as those which can be used for the reaction of the phosphorus oxychloride with the long-chain alcohol.

The addition of the basic substance raises the temperature. Care is taken to ensure that the temperature is kept in a range of between 0°C and 40°C, preferably between 10°C and 30°C and especially between 15°C and 20°C.

The reaction mixture is then stirred at 5°C to 30°C, preferably 15°C to 25°C (for example for 1 hour to 40 hours, preferably 3 hours to 15 hours).

The reaction mixture is hydrolyzed by the addition of water, during which the temperature should be kept at



between 10°C and 30°C, preferably between 15°C and 30°C and especially between 15°C and 20°C.

The above-mentioned hydrolyzing liquids can also contain
5 basic substances, such basic substances possibly being alkali metal and alkaline earth metal carbonates and bicarbonates.

To complete the hydrolysis, stirring is then continued for
10 a further 0.5 hour to 4 hours, preferably 1 to 3 hours and especially 1.5 to 2.5 hours, at 10°C to 30°C, preferably at 15°C to 25°C and especially at 18°C to 22°C.

The reaction solution is then washed with a mixture of
15 water and alcohols (preferably saturated aliphatic alcohols having 1 to 4 carbon atoms) which can optionally also contain a basic substance. The mixing ratio water:alcohol can be for example between 5 and 0.5, preferably 1 - 3 (v/v).

20 Examples of possible basic substances for the washing liquid are alkali metal and alkaline earth metal carbonates and bicarbonates, as well as ammonia (for example aqueous ammonia). A 3% solution of sodium carbonate in water is
25 particularly preferred.

The reaction solution can then optionally be washed with an acid solution. The acid washing is advantageous for removing basic components of the reaction solution which
30 have not yet reacted, especially when methylene chloride is used as the solvent.

The washing solution consists of a mixture of water and alcohols. Mixtures of saturated aliphatic alcohols having
35 1 to 4 carbon atoms are preferred, it optionally being possible for an acid substance to be present as well. The



mixing ratio water:alcohol can be for example between 5 and 0.5, preferably 1 - 3 (v/v).

Examples of possible acid substances for the washing liquid
5 are mineral acids and organic acids, for example hydrochloric acid, sulphuric acid, tartaric acid or citric acid. A 10% solution of hydrochloric acid in water is particularly preferred.

10 This is followed by a further washing with a mixture of water and alcohols. Mixtures of saturated aliphatic alcohols having 1 to 4 carbon atoms are preferred, it optionally being possible for a basic substance to be present as well. The mixing ratio water:alcohol can be for
15 example between 5 and 0.5, preferably 1 - 3.

The washed phases are then combined and dried in conventional manner, after which the solvent is removed (preferably under reduced pressure, for example at 5 to
20 100 mbar), optionally after the addition of 150 - 1000 ml, preferably 300 - 700 ml and especially 450 - 550 ml of an aliphatic alcohol (based on 1 molar part by weight of dry product). Preferred alcohols are saturated aliphatic alcohols with a chain length of 1 to 5 carbon atoms,
25 particularly preferred alcohols being n-butanol and isopropanol. The purpose of this alcohol treatment is the complete removal of residual water and the avoidance of foaming.

30 Further purification of the product can be effected for example by dissolving the crude product in hot ethanol, filtering off the residue and treating the filtrate with a mixed bed ion exchanger such as, for example, Amberlite MB3 in ethanolic solution. Any commercially available acid and
35 basic ion exchangers can be used, simultaneously or successively, instead of a mixed bed ion exchanger.



The solution is then recrystallized from ketones such as, for example, acetone or methyl ethyl ketone; digestion with the above solvents is sufficient in some cases. It may be convenient to purify the products by column chromatography or flash chromatography on silica gel using mixtures of chloroform, methylene chloride, methanol and 25% ammonia solution, for example, as the eluent.

Process variant B consists of the subsequent alkylation of products which are obtainable by process A using amino alcohols. Methyl p-toluenesulphonate or dimethyl sulphate are examples of alkylating agents which can be used. Possible solvents are those which have been mentioned above.

Alkali metal carbonates are examples of basic substances used. The reaction is carried out at elevated temperature, for example at the boiling point of the solvents.

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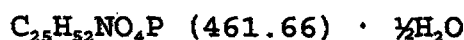
Examples:

Example 1: Name (IUPAC nomenclature)

4-(((Octadecyloxy)hydroxyphosphenyl)oxy) -
 1,1-dimethylpiperidinium hydroxide internal
 salt

Abbreviated name:

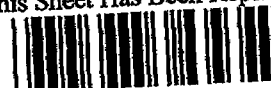
Octadecyl 1,1-dimethylpiperidinio-4-yl
 phosphate



Preparation variant A:

10.3 ml (0.11 mol) of phosphorus oxychloride are placed in
 100 ml of chloroform and cooled to 5 - 10°C. A solution of
 27.0 g (0.10 mol) of 1-octadecanol in 100 ml of chloroform
 and 35 ml of pyridine is added dropwise over 30 min, with
 stirring. After subsequent stirring for 30 min at
 5 - 10°C, 39.1 g (0.13 mol) of 4-hydroxy-1,1-dimethyl-
 piperidinium tosylate are added in a single portion. After
 the addition of 40 ml of pyridine and 30 ml of DMF, the
 mixture is stirred for 24 h at room temperature. It is
 then hydrolyzed with 15 ml of water and subsequently
 stirred for 30 min and the organic phase is washed with
 200 ml each of water/ methanol (1:1), 3% Na₂CO₃/methanol
 (1:1) and finally water/methanol (1:1). The organic phase
 is concentrated, the residue is dissolved in 300 ml of hot
 ethanol and the solution is filtered after cooling. The
 filtrate is stirred with 80 g of Amberlite MB3 ion
 exchanger, the mixture is filtered and the filtrate is
 concentrated. The residue is recrystallized from 300 ml of
 methyl ethyl ketone, filtered off with suction and dried
 under vacuum over P₂O₅.

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Yield: 4.71 g (10%)

Elemental analysis:

5	C	H	N
calc.:	65.26%	11.63%	2.62%
found:	64.38%	11.61%	2.73%
	65.04%	11.80%	2.78%

10 Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

$R_f = 0.17$

(1-butanol/glacial acetic acid/water 40:10:10)

15 $R_f = 0.12$

Melting point: 270 - 271°C (decomposition)

20 Preparation variant B:

20.1 ml (0.22 mol) of phosphorus oxychloride are placed in
100 ml of methylene chloride and cooled to 5 - 10°C and a
solution of 54.1 g (0.20 mol) of octadecanol in 400 ml of
25 methylene chloride and 70.5 ml of pyridine is added over
30 min, with stirring. After subsequent stirring for one
hour, 29.9 g (0.26 mol) of 4-hydroxy-1-methylpiperidine in
80 ml of pyridine are added dropwise. After stirring for
3 h at 10°C, the mixture is hydrolyzed with 30 ml of water
30 while being cooled with ice and is subsequently stirred for
one hour. The organic phase is washed with 200 ml each of
water/methanol (1:1), 3 percent hydrochloric acid/ methanol
(1:1) and water/methanol (1:1). The organic phase is dried
over Na_2SO_4 and concentrated until turbidity appears, and
35 1 l of methyl ethyl ketone is added. The crystals are
recrystallized from 1 l of methyl ethyl ketone, filtered
off with suction and dried under vacuum over P_2O_5 .



Yield: 54.1 g (60%) of octadecyl 1-methylpiperidinio-4-yl phosphate

5 98.1 g (0.22 mol) of octadecyl 1-methylpiperidinio-4-yl phosphate are suspended in 500 ml of absolute ethanol and heated to boiling. Under reflux, a total of 71.8 g (0.39 mol) of methyl p-toluenesulphonate and 26.5 g (0.19 mol) of potassium carbonate are added alternately in eight portions
10 over 2 h. When the addition is complete, the mixture is refluxed for a further hour. After cooling, it is filtered, the filtrate is concentrated to half and 150 g of moist Amberlite MB3 ion exchanger are added to the solution. After stirring for two hours, the mixture is
15 filtered with suction over kieselguhr/activated charcoal and the filtrate is concentrated and crystallized with acetone. The crystal cake is recrystallized from methyl ethyl ketone and dried under vacuum over P_2O_5 .

20 Yield: 46.1 g (46%) of octadecyl 1,1-dimethylpiperidinio-4-yl phosphate

Elemental analysis:

25	C	H	N
calc.:	65.26%	11.63%	2.62%
found:	65.18%	11.62%	2.68%
	65.07%	11.71%	2.70%

30 Melting point: 271 - 272°C (decomposition)

Example 2: Hexadecyl piperidinio-4-yl phosphate

35 $C_{21}H_{44}NO_4P$ (405.558)

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7.1 ml (77 mmol) of phosphorus oxychloride are dissolved in 50 ml of dry tetrahydrofuran and, after cooling to 5 - 10°C, a solution of 17 g (70 mmol) of hexadecanol and 48 ml of triethylamine in 150 ml of tetrahydrofuran is added dropwise, with stirring. When the addition is complete, the mixture is subsequently stirred for 30 min in an ice bath and then left to warm up to room temperature. 10.1 g (100 mmol) of 4-piperidinol are dissolved in 100 ml of tetrahydrofuran and mixed with 17 ml of triethylamine and the mixture is added dropwise to the reaction solution, with stirring, so that the temperature does not exceed 40°C. When the addition is complete, the mixture is refluxed for one hour. While still hot, the solution is separated from the triethylammonium chloride by filtration and, after cooling, is poured into an ice/2 M hydrochloric acid mixture, with stirring. The product obtained on cooling in a refrigerator is taken up in methylene chloride, dried over MgSO_4 , concentrated and chromatographed on silica gel with methylene chloride/methanol/ 25% ammonia (70:30:5). The product fractions are combined and concentrated. After recrystallization from methanol, the product is dried under vacuum over P_2O_5 .

Yield: 10.0 g (35%)

25

Elemental analysis:

	C	H	N
calc.:	62.19%	10.94%	3.45%
30 found:	65.15%	11.14%	3.54%
	62.41%	11.19%	3.34%

Thin layer chromatogram:

(chloroform/methanol/25% ammonia 70:20:10)

35 $R_f = 0.42$

(1-butanol/glacial acetic acid/water 40:10:10)

$R_f = 0.33$

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Example 3: Hexadecyl 1,1-dimethylpiperidinio-4-yl
phosphate



5

5.7 g (14 mmol) of hexadecyl piperidinio-4-yl phosphate are dissolved in 100 ml of methanol and mixed with 11.6 g (84 mmol) of potassium carbonate. 4.0 ml (42 mmol) of dimethyl sulphate are added dropwise over 30 min, with
10 thorough stirring. The mixture is subsequently stirred for 4 h at 40°C, cooled, filtered and concentrated. The residue is digested with acetone and, after filtration with suction, is dissolved in 100 ml of 96% ethanol. 15 g of Amberlite MB3 ion exchanger are added and the mixture is
15 stirred for 3 h. After filtration, the filtrate is concentrated and recrystallized twice from methyl ethyl ketone. The crystals are dried under vacuum over P_2O_5 .

Yield: 3.70 g (61%)

20

Elemental analysis:

	C	H	N
25 calc.:	61.17%	11.16%	3.10%
found:	60.83%	11.14%	2.99%
	60.92%	11.26%	3.00%

Thin layer chromatogram:

30 (chloroform/methanol/25% ammonia 70:20:10)

$R_f = 0.28$

(1-butanol/glacial acetic acid/water 40:10:10)

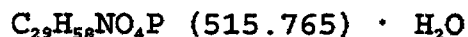
$R_f = 0.13$

35 Melting point: 230°C (decomposition)

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Example 4: Erucyl 1,1-dimethylpiperidinio-4-yl phosphate



5 10.3 ml (0.11 mol) of phosphorus oxychloride are placed in
50 ml of chloroform, and a solution of 32.5 g (0.10 mol) of
erucyl alcohol and 32 ml of pyridine in 100 ml of
chloroform is added dropwise at 5 - 10°C. After subsequent
stirring for half an hour, 39.1 g (0.13 mol) of 4-hydroxy-
10 1,1-dimethylpiperidinium tosylate are added in a single
portion. After the dropwise addition of 40 ml of pyridine,
the mixture is left to warm up to room temperature and
stirred for 3 h. It is then hydrolyzed with 15 ml of
water, subsequently stirred for half an hour and washed
15 with 100 ml each of water/methanol (1:1), 3% sodium
carbonate solution/methanol (1:1), 3% citric acid/methanol
(1:1) and water/methanol (1:1). The residue obtained after
concentration of the organic phase is digested with acetone
and then dissolved in 150 ml of 96% ethanol. This solution
20 is stirred for 3 h with 20 g of Amberlite MB3 ion exchanger
and filtered over kieselguhr to give a clear solution.
This is concentrated and chromatographed on silica gel with
chloroform/ methanol/25% ammonia 70:40:10. The product
fractions are combined and concentrated to dryness under
25 vacuum.

30

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Yield: 4.4 g (9%)

Elemental analysis:

5	C	H	N
calc.:	65.26%	11.63%	2.62%
found:	64.38%	11.61%	2.73%
	65.04%	11.80%	2.78%

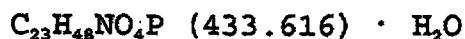
10 Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:20:10)

$R_f = 0.30$

15

Example 5: Hexadecyl 1,1-dimethylpiperidinio-3-yl
phosphate



20 10.3 ml (0.11 mol) of phosphorus oxychloride are placed in
50 ml of chloroform and cooled to 0 - 10°C. 24.2 g
(0.10 mol) of n-hexadecanol are dissolved in 100 ml of
chloroform, 32 ml of pyridine are added and the mixture is
added dropwise to the phosphorus oxychloride solution over
25 one hour, with ice cooling. After subsequent stirring for
half an hour, 39.2 g (0.13 mol) of 3-hydroxy-1,1-dimethyl-
piperidinium tosylate are added in a single portion and
40 ml of pyridine are added dropwise over 15 min at room
temperature. After stirring for 16 h at room temperature,
30 the mixture is hydrolyzed with 15 ml of water, stirred for
half an hour and washed with 100 ml each of water/ methanol
(1:1), 3% sodium carbonate solution/ methanol (1:1),
3% citric acid/methanol (1:1) and water/ methanol (1:1).
The organic phase is dried over sodium sulphate and
35 concentrated. The residue is dissolved in 150 ml of 96%
ethanol, the solution is filtered and the filtrate is
stirred with Amberlite MB3 ion exchanger. After the ion

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exchanger has been filtered off, the filtrate is concentrated and the residue is crystallized with acetone, filtered off with suction and dried under vacuum over P_2O_5 .

5 Yield: 13.5 g (31%)

Elemental analysis:

	C	H	N
10 calc.:	61.17%	11.16%	3.10%
found:	60.78%	11.41%	2.87%
	60.85%	11.31%	2.86%

Thin layer chromatogram:

15 (chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)
 $R_f = 0.37$

20

25

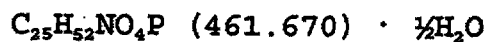
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Example 6: Octadecyl 1,1-dimethylpiperidinio-3-yl
phosphate



5

This is prepared analogously to Example 5 from 10.3 ml (0.11 mol) of phosphorus oxychloride, 27.0 g (0.10 mol) of octadecanol, 32 + 40 ml of pyridine and 39.2 g (0.13 mol) of 3-hydroxy-1,1-dimethylpiperidinium tosylate.

10

Yield: 18.7 g (40%)

Elemental analysis:

15		C	H	N
	calc.:	63.80%	11.35%	2.98%
	found:	63.38%	11.72%	2.63%
		63.61%	11.98%	2.61%

20 Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

$R_f = 0.35$

25

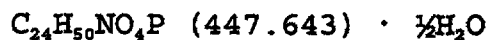
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Example 7: Hexadecyl (1,1-dimethylpiperidinio-2-yl)
methyl phosphate



5

This is prepared analogously to Example 5 from 10.3 ml (0.11 mol) of phosphorus oxychloride, 24.2 g (0.10 mol) of hexadecanol, 32 + 40 ml of pyridine and 41.0 g (0.13 mol) of 2-hydroxymethyl-1,1-dimethylpiperidinium tosylate.

10

Yield: 22.9 g (51%)

Elemental analysis:

15

	C	H	N
calc.:	63.13%	11.26%	3.07%
found:	63.69%	11.73%	3.04%
	63.75%	11.71%	3.04%

20

Thin layer chromatogram:
(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)
 $R_f = 0.47$

25

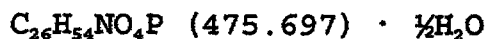
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Example 8: Octadecyl (1,1-dimethylpiperidinio-2-yl)
methyl phosphate



5

This is prepared analogously to Example 5 from 10.3 ml (0.11 mol) of phosphorus oxychloride, 27.0 g (0.10 mol) of octadecanol, 32 + 40 ml of pyridine and 41.0 g (0.13 mol) of 2-hydroxymethyl-1,1-dimethylpiperidinium tosylate.

10

Yield: 23.9 g (50%)

Elemental analysis:

15

	C	H	N
calc.:	64.43%	11.44%	2.89%
found:	64.50%	11.61%	2.67%
	64.11%	11.49%	2.77%

20 Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

$R_f = 0.47$

25

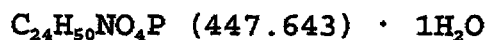
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Example 9: Hexadecyl (1,1-dimethylpiperidinio-3-yl)
methyl phosphate



5

This is prepared analogously to Example 5 from 10.3 ml (0.11 mol) of phosphorus oxychloride, 24.2 g (0.10 mol) of hexadecanol, 32 + 40 ml of pyridine and 41.0 g (0.13 mol) of 3-hydroxymethyl-1,1-dimethylpiperidinium tosylate.

10

Yield: 17.2 g (39%)

Elemental analysis:

15

	C	H	N
calc.:	61.91%	11.26%	3.01%
found:	62.32%	12.21%	2.86%
	61.79%	11.96%	2.98%

20 Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

$R_f = 0.29$

25

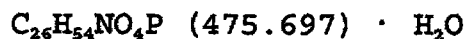
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Example 10: Octadecyl (1,1-dimethylpiperidinio-3-yl)
methyl phosphate



5

This is prepared analogously to Example 5 from 10.3 ml (0.11 mol) of phosphorus oxychloride, 27.0 g (0.10 mol) of octadecanol, 32 + 40 ml of pyridine and 41.0 g (0.13 mol) of 3-hydroxymethyl-1,1-dimethylpiperidinium tosylate.

10

Yield: 16.7 g (35%)

Elemental analysis:

15

	C	H	N
calc.:	63.25%	11.43%	2.84%
found:	62.98%	12.21%	2.76%
	63.67%	12.47%	2.80%

20

Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

$R_f = 0.30$

25

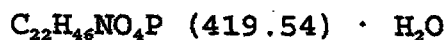
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Example 11: Tetradecyl 1,1-dimethylhexahydroazepinio-
4-yl phosphate



5

This is prepared analogously to Example 5 from 9.6 g
(45 mmol) of tetradecanol, 4.6 ml (50 mmol) of phosphorus
oxychloride, 10 + 20 ml of pyridine and 21.3 g (67.5 mmol)
of hydroxy-1,1-dimethylhexahydroazepinium tosylate. It is
10 purified by flash chromatography on silica gel with
methylene chloride/methanol/ 25% ammonia 70:40:10.

Yield: 2.70 g (15%)

15

Elemental analysis:

	C	H	N
calc.:	60.40%	11.05%	3.20%
20 found:	60.47%	11.29%	3.63%
	60.78%	11.52%	3.68%

Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
25 70:40:10)

$R_f = 0.30$

(1-butanol/glacial acetic acid/water 40:10:10)

$R_f = 0.08$

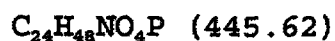
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Example 12: Hexadecyl 1,1-dimethylhexahydroazepinio-
4-yl phosphate



5

This is prepared analogously to Example 5 from 10.8 g
(45 mmol) of hexadecanol, 4.6 ml (50 mmol) of phosphorus
oxychloride, 10 + 20 ml of pyridine and 21.3 g (67.5 mmol)
of 4-hydroxy-1,1-dimethylhexahydroazepinium tosylate. It
10 is purified by flash chromatography on silica gel with
methylene chloride/methanol/ 25% ammonia 70:30:10.

Yield: 5.0 g (25%)

15 Elemental analysis:

	C	H	N
calc.:	64.69%	10.86%	3.14%
found:	63.90%	11.54%	3.22%
	64.08%	11.59%	3.24%

20

Thin layer chromatogram:

(chloroform/methanol/25% ammonia 80:25:5)

$R_f = 0.10$

(1-butanol/glacial acetic acid/water 40:10:10)

25 $R_f = 0.10$

Melting point: >250°C (decomposition)

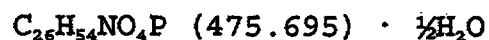
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Example 13: Octadecyl 1,1-dimethylhexahydroazepinio-
4-yl phosphate



5

This is prepared analogously to Example 5 from 12.1 g
(45 mmol) of octadecanol, 4.6 ml (50 mmol) of phosphorus
oxychloride, 10 + 20 ml of pyridine and 21.3 g (67.5 mmol)
of 4-hydroxy-1,1-dimethylhexahydroazepinium tosylate. It
10 is purified by flash chromatography on silica gel with
methylene chloride/methanol/ 25% ammonia 70:30:10.

Yield: 5.5 g (26%)

15 Elemental analysis:

	C	H	N
calc.:	64.43%	11.44%	2.89%
found:	64.54%	11.64%	2.82%
20	64.66%	11.58%	2.64%

Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

25 $R_f = 0.22$

Melting point: >250°C (decomposition)

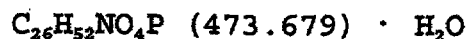
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Example 14: Cis- Δ^9 -octadecenyl 1,1-dimethylhexahydro
azepinio-4-yl phosphate



5

This is prepared analogously to Example 5 from 12.1 g
(45 mmol) of cis- Δ^9 -octadecenol, 4.6 ml (50 mmol) of
phosphorus oxychloride, 10 + 20 ml of pyridine and 21.3 g
(67.5 mmol) of 4-hydroxy-1,1-dimethylhexahydroazepinium
10 tosylate. It is purified by flash chromatography on silica
gel with methylene chloride/ methanol/25% ammonia 70:30:10.

Yield: 4.5 g (21%)

15 Elemental analysis:

	C	H	N
calc.:	63.51%	11.07%	2.85%
found:	64.05%	11.21%	3.10%
20	63.80%	11.06%	3.06%

Thin layer chromatogram:

(chloroform/methanol/25% ammonia 70:40:10)

$R_f = 0.28$

25 (1-butanol/glacial acetic acid/water 40:10:10)

$R_f = 0.10$

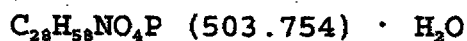
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Example 15: Eicosyl 1,1-dimethylhexahydroazepinio-4-yl
phosphate



5

This is prepared analogously to Example 5 from 13.4 g
(45 mmol) of eicosanol, 4.6 ml (50 mmol) of phosphorus
oxychloride, 10 + 20 ml of pyridine and 21.3 g (67.5 mmol)
of 4-hydroxy-1,1-dimethylhexahydroazepinium tosylate. It
10 is purified by flash chromatography on silica gel with
methylene chloride/methanol/ 25% ammonia 70:30:10.

Yield: 5.7 g (25%)

15 Elemental analysis:

	C	H	N
calc.:	64.46%	11.59%	2.68%
found:	63.51%	11.48%	2.95%
20	64.00%	11.79%	2.91%

Thin layer chromatogram:

(chloroform/methanol/25% ammonia 70:40:10)

$R_f = 0.12$

25

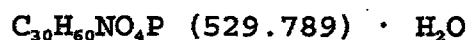
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Example 16: Erucyl 1,1-dimethylhexahydroazepinio-4-yl
phosphate



5

This is prepared analogously to Example 5 from 16.2 g
(50 mmol) of erucyl alcohol, 5.1 ml (55 mmol) of phosphorus
oxychloride, 18 + 30 ml of pyridine and 20.5 g (65 mmol) of
4-hydroxy-1,1-dimethylhexahydroazepinium tosylate. It is
10 purified by flash chromatography on silica gel with
methylene chloride/methanol/ 25% ammonia 70:30:10.

Yield: 4.1 g (15%)

15 Elemental analysis:

	C	H	N
calc.:	65.78%	11.41%	2.56%
found:	65.76%	12.01%	2.97%
20	65.82%	11.63%	2.96%

Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

25 $R_f = 0.30$

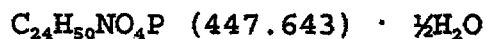
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Example 17: Octadecyl 1,1-dimethylpyrrolidinio-3-yl
phosphate



5

This is prepared analogously to Example 5 from 3.25 g
(12 mmol) of octadecanol, 1.21 ml (13 mmol) of phosphorus
oxychloride, 3.7 + 4.8 ml of pyridine and 4.31 g (15 mmol)
of hydroxy-1,1-dimethylpyrrolidinium tosylate. The crude
10 product is purified by dissolution in 96% ethanol and
treatment with Amberlite MB3 ion exchanger.

Yield: 1.31 g (25%)

15 Elemental analysis:

	C	H	N
calc.:	63.13%	11.26%	3.07%
found:	62.99%	11.28%	2.80%
20	62.74%	11.27%	2.89%

Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

25 $R_f = 0.25$

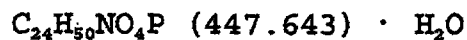
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Example 18: Hexadecyl 2-(1,1-dimethylpyrrolidinio-
2-yl)ethyl phosphate



5

This is prepared analogously to Example 5 from 9.21 g
(38 mmol) of hexadecanol, 3.9 ml (42 mmol) of phosphorus
oxychloride, 13 + 16 ml of pyridine and 15.8 g (50 mmol) of
2-(2-hydroxyethyl)-1,1-dimethylpyrrolidinium tosylate. It
10 is purified by dissolution in 96% ethanol and treatment
with Amberlite MB3 ion exchanger.

Yield: 6.0 g (35%)

15 Elemental analysis:

	C	H	N
calc.:	61.91%	11.26%	3.01%
found:	61.82%	11.69%	3.21%
20	61.93%	11.86%	3.28%

Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

25 $R_f = 0.38$

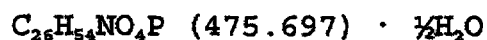
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Example 19: Octadecyl 2-(1,1-dimethylpyrrolidinio-
2-yl)ethyl phosphate



5

This is prepared analogously to Example 5 from 10.3 g
(38 mmol) of octadecanol, 3.9 ml (42 mmol) of phosphorus
oxychloride, 13 + 16 ml of pyridine and 15.8 g (50 mmol) of
2-(2-hydroxyethyl)-1,1-dimethylpyrrolidinium tosylate. It
10 is purified by dissolution in 96% ethanol and treatment
with Amberlite MB3 ion exchanger.

Yield: 7.8 g (43%)

15 Elemental analysis:

	C	H	N
calc.:	64.43%	11.44%	2.89%
found:	64.69%	11.77%	2.64%
20	64.84%	11.88%	2.69%

Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

25 $R_f = 0.35$

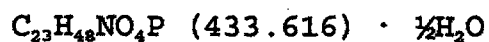
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Example 20: Hexadecyl (1,1-dimethylpyrrolidinio-2-yl)
methyl phosphate



5

This is prepared analogously to Example 5 from 9.21 g
(38 mmol) of hexadecanol, 3.9 ml (42 mmol) of phosphorus
oxychloride, 13 + 16 ml of pyridine and 15.1 g (50 mmol) of
2-hydroxymethyl-1,1-dimethylpyrrolidinium tosylate. It is
10 purified by dissolution in 96% ethanol and treatment with
Amberlite MB3 ion exchanger.

Yield: 8.3 g (51%)

15 Elemental analysis:

	C	H	N
calc.:	62.41%	11.16%	3.16%
found:	62.09%	11.48%	3.01%
20	62.25%	11.66%	3.09%

Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

25 $R_f = 0.33$

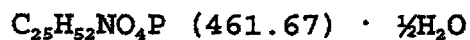
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Example 21: Octadecyl (1,1-dimethylpyrrolidinio-2-yl)
methyl phosphate



5

This is prepared analogously to Example 5 from 10.3 g
(38 mmol) of octadecanol, 3.9 ml (42 mmol) of phosphorus
oxychloride, 13 + 16 ml of pyridine and 15.1 g (50 mmol) of
2-hydroxymethyl-1,1-dimethylpyrrolidinium tosylate. It is
10 purified by dissolution in 96% ethanol and treatment with
Amberlite MB3 ion exchanger.

Yield: 9.0 g (52%)

15 Elemental analysis:

	C	H	N
calc.:	63.80%	11.35%	2.98%
found:	63.13%	11.57%	2.84%
20	63.55%	11.66%	2.82%

Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

25 $R_f = 0.35$

30

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Example 22: Hexadecyl 1-methylquinuclidinio-
3-yl phosphate



5

2.7 ml (30 mmol) of phosphorus oxychloride are dissolved in 25 ml of chloroform and cooled to 5 - 10°C and a solution of 6.4 g (26 mmol) of hexadecanol and 10 ml of pyridine in 50 ml of chloroform is added dropwise over one hour. After
10 subsequent stirring for half an hour at room temperature, a solution of 4.5 g (35 mmol) of 3-hydroxyquinuclidine and 5 ml of pyridine in 10 ml of chloroform is added. After stirring for 5 h at room temperature, the mixture is hydrolyzed with 15 ml of water and subsequently stirred for
15 half an hour. It is then washed twice with 100 ml of water/methanol (1:1) and the organic phase is dried over magnesium sulphate and concentrated to dryness. The residue is chromatographed on silica gel with methylene chloride/methanol 80:25 and then methylene chloride/
20 methanol/25% ammonia 80:25:5. The product fractions are purified, evaporated to dryness and crystallized with acetone. The crystals are dried under vacuum over P_2O_5 .

Yield: 4.95 g (44%) of hexadecyl quinuclidinio-3-yl
25 phosphate

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4.95 g (11.5 mmol) of hexadecyl quinuclidinio-3-yl phosphate are dissolved in 30 ml of methanol, 13.7 g (69 mmol) of potassium carbonate and 8.5 ml of water are added and a solution of 3.3 ml (35 mmol) of dimethyl sulphate in 5 ml of methanol is added dropwise, with thorough stirring. After stirring for 14 h at room temperature, the inorganic salts are filtered off, the filtrate is concentrated to dryness and the residue is taken up in methylene chloride. After filtration, the filtrate is chromatographed on silica gel with methylene chloride/methanol/25% ammonia 70:30:5. The product fractions are combined, evaporated to dryness and stirred with acetone until crystallization occurs. The crystals are dried under vacuum over P_2O_5 .

15

Yield: 2.7 g (49%)

Elemental analysis:

20	C	H	N
calc.:	60.99%	10.88%	2.96%
found:	61.38%	11.04%	3.29%
	61.46%	11.22%	3.25%

25 Thin layer chromatogram:

(chloroform/methanol/25% ammonia 70:40:10)

$R_f = 0.44$

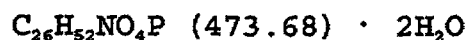
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Example 23: Octadecyl 1-methylquinuclidinio-
3-yl phosphate



5

This is prepared analogously to Example 5 from 18.3 g (67.5 mmol) of octadecanol, 7.0 ml (75 mmol) of phosphorus oxychloride, 18 + 20 ml of pyridine and 28.3 g (90 mmol) of 3-hydroxy-1-methylquinuclidinium tosylate. It is purified
10 by dissolution in 96% ethanol and treatment with Amberlite MB3 ion exchanger.

Yield: 18.4 g (57%)

15 Elemental analysis:

	C	H	N
calc.:	61.27%	11.07%	2.75%
found:	61.27%	10.91%	2.45%
20	61.95%	11.23%	2.51%

Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

25 $R_f = 0.37$

(1-butanol/glacial acetic acid/water 40:10:10)

 $R_f = 0.13$

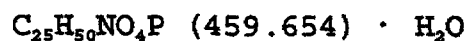
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Example 24: Hexadecyl 1,1-dimethyltropanio-4-yl phosphate



5 This is prepared analogously to Example 5 from 12.1 g
(50 mmol) of hexadecanol, 5.1 ml (55 mmol) of phosphorus
oxychloride, 17 + 40 ml of pyridine and 21.3 g (65 mmol) of
4-hydroxy-1,1-dimethyltropanium tosylate. It is purified
by dissolution in 96% ethanol, treatment with Amberlite MB3
10 ion exchanger and recrystallization from acetone.

Yield: 11.3 g (49%)

Elemental analysis:

15

	C	H	N
calc.:	62.86%	10.97%	2.93%
found:	62.45%	11.52%	2.82%
	62.58%	11.52%	2.75%

20

Thin layer chromatogram:

(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)

$R_f = 0.28$

25

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Example 25: Octadecyl 1,1-dimethyltropanio-4-yl phosphate



- 5 This is prepared analogously to Example 5 from 13.5 g
(50 mmol) of octadecanol, 5.1 ml (55 mmol) of phosphorus
oxychloride, 17 + 20 ml of pyridine and 21.3 g (65 mmol) of
4-hydroxy-1,1-dimethyltropanium tosylate. It is purified
by dissolution in 96% ethanol and treatment with Amberlite
10 MB3 ion exchanger.

Yield: 10.7 g (44%)

Elemental analysis:

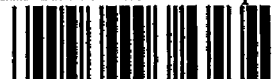
15	C	H	N
calc.:	66.49%	11.16%	2.87%
found:	65.72%	11.48%	2.64%
	66.27%	11.78%	2.65%

- 20 Thin layer chromatogram:
(chloroform/methanol/1 M sodium acetate in 25% ammonia
70:40:10)
 $R_f = 0.22$

25

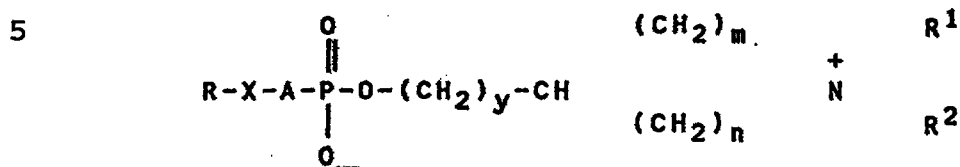
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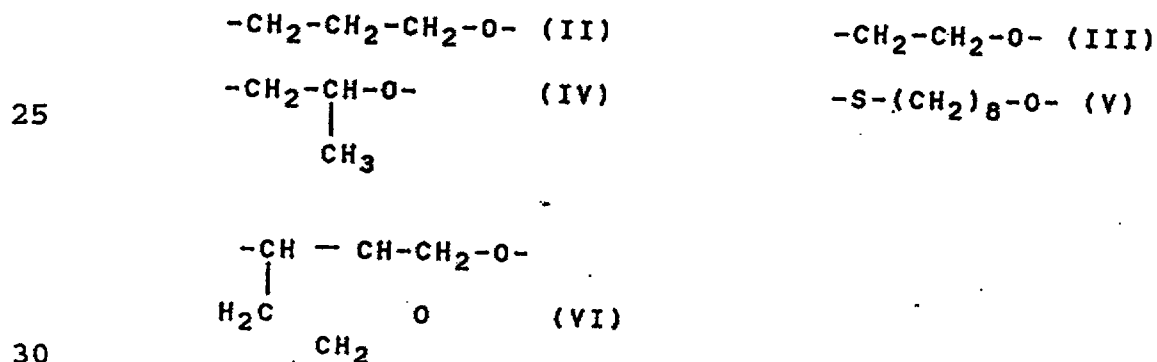
Claims

1. Compounds of general formula I:



in which R is a linear or branched alkyl radical having 10 to 24 carbon atoms, which can also contain one to three double or triple bonds, R¹ and R² independently of one another are hydrogen or in each case a linear, branched or cyclic saturated or unsaturated alkyl radical having 1 to 6 carbon atoms, which can also contain a Cl, OH or NH₂ group, it also being possible for two of these radicals to be bonded together to form a ring,

A is a single bond or one of the groups of the formulae



the groups (II) to (VI) being orientated in such a way that the oxygen atom is bonded to the phosphorus atom of compound (I),

X is an oxygen or sulphur atom or NH when A is a single bond, or an oxygen or sulphur atom when A is one of the groups (II) to (IV),

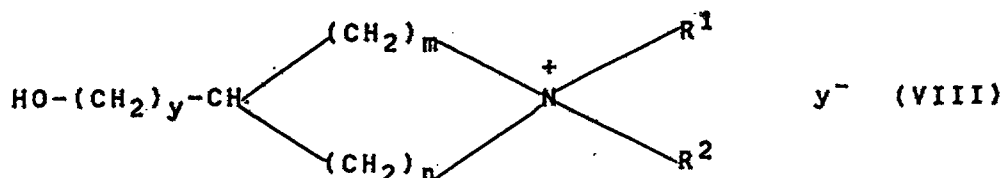


y is equal to 0 or a natural number between 1 and 3,
and
m and n independently of one another are 0 or natural
numbers, with the proviso that $m + n = 2$ to 8.

- 5 2. Compounds according to Claim 1, characterized in that
X is an oxygen atom.
3. Compounds according to Claim 1 or 2, characterized in
10 that A is a single bond.
4. Compounds according to Claims 1 to 3, characterized
in that R^1 and R^2 are each methyl groups.
- 15 5. Octadecyl 1,1-dimethylpiperidinio-4-yl phosphate and
octadecyl 1,1-dimethylhexahydroazepinio-4-yl
phosphate.
6. A process for the preparation of a compound according
20 to one of Claims 1 to 5, characterized in that a
compound of the general formula



- 25 in which R, X and A are as defined in Claim 1, is
reacted with phosphorus oxytrichloride in the
presence of a suitable auxiliary base, with or
without a solvent, and then reacted with a compound
of the general formula

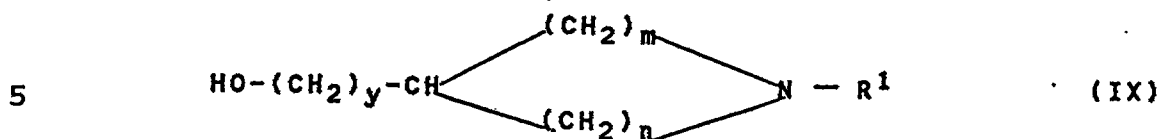


35 in which R^1 , R^2 , y, m and n are as defined in Claim 1
and Y is halide, mesylate or tosylate, to give





compounds of the general formula I, or optionally
compounds of the general formula



10 in which R^1 , y , m and n are as defined in Claim 1, can
be reacted, compounds of general formula (I) in which
 R^1 and/or R^2 are hydrogen being reacted with
alkylating agents R^2-Y , in which R^2 is as defined in
Claim 1 and Y is Cl, bromine, iodine, tosyl or mesyl,
in a manner known *per se*.

15

7. A process for the purification of the compounds of
formula I, characterized in that a solution of the
compounds of formula I, which have been prepared by
means of known processes or by a process according to
20 Claim 5, in an organic solvent is treated with a
mixed bed ion exchanger or successively or
simultaneously with an acid or basic ion exchanger.

8. A drug, characterized in that it contains as the
25 active ingredient one or more compounds according to
one of Claims 1 to 5 or a pharmaceutically acceptable
salt thereof, optionally together with pharma-
ceutically conventional excipients, adjuncts, fillers
and diluents, the amount of active ingredient being
30 between 50 mg and 250 mg.

35





9. A drug according to Claim 7, characterized in that it contains as the active ingredient octadecyl 1,1-dimethylpiperidinio-4-yl phosphate, octadecyl 1,1-dimethylperhydroazepinio-4-yl phosphate, erucyl 1,1-dimethylpiperidinio-4-yl phosphate or erucyl 1,1-dimethylperhydroazepinio-4-yl phosphate, the amount of active ingredient being between 50 mg and 250 mg.
10. A drug according to Claim 8, characterized in that it contains as the active ingredient octadecyl 1,1-dimethylpiperidinio-4-yl phosphate, the amount of active ingredient being between 50 mg and 250 mg.
11. Use of drugs according to one of Claims 8 or 9 for combating tumours.
12. Use of a drug according to one of Claims 8 or 9 for combating protozoal and fungal diseases, especially leishmaniasis.
13. Use of a drug according to one of Claims 8 or 9 for the therapy of autoimmune diseases, especially multiple sclerosis.
14. Use of a drug according to one of Claims 8 or 9 for the therapy of skin diseases, especially psoriasis.
15. Use of a drug according to one of Claims 8 or 9 for the therapy of bone marrow damage due to treatment with cytostatic agents and other myelotoxic active ingredients.
16. Use of a drug according to one of Claims 8 or 9 for the therapy of viral diseases and *inter alia* for the therapy of AIDS.



17. A process for the preparation of an antitumoural agent, characterized in that a formulation is prepared which contains as the active ingredient one or more compounds according to one of Claims 1 to 5, optionally together with pharmaceutically conventional excipients, adjuncts, fillers and diluents.

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