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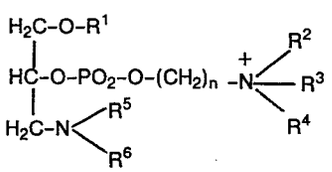
(54) 1-O-Alkyl-3-amino-propan-1.2-diol-2-O-phospholipids, process for producing the same and pharmaceutical preparations containing the same.

(57) The invention is related to 1-O-alkyl-3-amino-propan-1.2-diol-2-O-phospholipids having the formula I



I

process for producing the same and pharmaceutical preparations containing the same.

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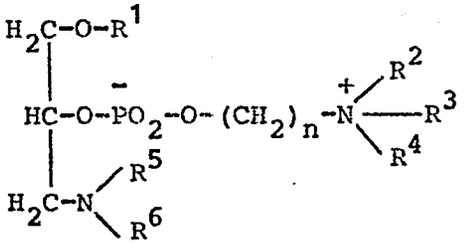
Specification

The present invention is related to 1-O-alkyl-3-amino-propan-1.2-diol-2-O-phospholipids, processes for producing the same and their use as active agents in drugs, in particular for the treatment of high blood pressure, atherosklerosis and asthma as well as for their application with diseases of the immuno system and for the treatment of cancer.

The 1-O-alkyl-3-amino-propan-1.2-diol-2-O-phospholipids according to the present invention correspond to the formula I



I

wherein

R^1 is a saturated or unsaturated, straight-chain or branched alkyl group with 1o to 2o carbon atoms,

R^2, R^3 and R^4 which may be the same or different, represent hydrogen or a lower alkyl group with 1 to 4 carbon atoms,

R^5 and R^6 which may be the same or different, represent hydrogen or the group $-A-C_mH_{2m}-R^7$ or $-A-C_mH_{2m-2}-R^7$,

R^7 is hydrogen, unsubstituted phenyl or phenyl substituted by a C_{1-3}-alkyl, C_{1-3}-alkoxy, trifluoromethyl group, or a halogen atom,

A is a bond, -CO-, -COO- or $-CONR^8-$,

R^8 is hydrogen or C_{1-4}-alkyl,

m is a numeral from 0 to 2o and

n is a numeral from 2 to 4.

Preferred are those compounds of formula I wherein R^1 is a saturated straight-chained alkyl group with 1o to 2o carbon atoms or an unsaturated straight-chained alkyl group with 1 or 2 double bonds and 1o to 2o carbon atoms, R^2, R^3 and R^4 which may be the same or different from each other, represent hydrogen or a methyl group, R^5 and R^6 which may be the same or different from each other, represent hydrogen or the group $-A-(CH_2)_m-R^7$, R^7 is hydrogen, unsubstituted phenyl or phenyl substituted by a methyl, methoxy or trifluoromethyl group or a halogen atom, A represents a bond, -CO-, -COO- or $-CONR^8-$, R^8 is hydrogen or C_{1-4}-alkyl, m is an integer from 0 to 2o, if R^7 is hydrogen, or is an integer from 0 to 2, if R^7 is phenyl unsubstituted or substituted as indicated, and n is 2. Most preferred under those compounds are the compounds of formula I wherein R^1 is a saturated straight-chained alkyl group having from 1o to 2o carbon atoms while R^2, R^3, R^4, R^5, R^6, R^7, R^8, m and n have the same meaning as indicated in connection with the preferred group of compounds.

Compounds according to the present invention are for instance:

3-Amino-1-O-decyl-propan-1.2-diol-2-O-phosphocholine
3-Amino-1-O-undecyl-propan-1.2-diol-2-O-phosphocholine
3-Amino-1-O-dodecyl-propan-1.2-diol-2-O-phosphocholine
3-Amino-1-O-tridecyl-propan-1.2-diol-2-O-phosphocholine
3-Amino-1-O-tetradecyl-propan-1.2-diol-2-O-phosphocholine
3-Amino-1-O-pentadecyl-propan-1.2-diol-2-O-phosphocholine
3-Amino-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine
3-Amino-1-O-heptadecyl-propan-1.2-diol-2-O-phosphocholine
3-Amino-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine
3-Amino-1-O-nonadecyl-propan-1.2-diol-2-O-phosphocholine
3-Amino-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine
1-O-Decyl-3-methylamino-propan-1.2-diol-2-O-phosphocholine
1-O-Dodecyl-3-methylamino-propan-1.2-diol-2-O-phosphocholine
3-Methylamino-1-O-tetradecyl-propan-1.2-diol-2-O-phosphocholine
1-O-Hexadecyl-3-methylamino-propan-1.2-diol-2-O-phosphocholine

3-Methylamino-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-methylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Decyl-3-ethylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Dodecyl-3-ethylamino-propan-1.2-diol-2-O-phosphocholine

3-Ethylamino-1-O-tetradecyl-propan-1.2-diol-2-O-phosphocholine

3-Ethylamino-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-Ethylamino-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-ethylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Decyl-3-hexadecylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Dodecyl-3-hexadecylamino-propan-1.2-diol-2-O-phosphocholine

3-Hexadecylamino-1-O-tetradecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-hexadecylamino-propan-1.2-diol-2-O-phosphocholine

3-Hexadecylamino-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-hexadecylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Decyl-3-octadecylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Dodecyl-3-octadecylamino-propan-1.2-diol-2-O-phosphocholine

3-Octadecylamino-1-O-tetradecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Octadecyl-3-octadecylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-octadecylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Decyl-3-eicosylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Dodecyl-3-eicosylamino-propan-1.2-diol-2-O-phosphocholine

3-Eicosylamino-1-O-tetradecyl-propan-1.2-diol-2-O-phosphocholine

3-Eicosylamino-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-eicosylamino-propan-1.2-diol-2-O-phosphocholine

3-Benzylamino-1-O-decyl-propan-1.2-diol-2-O-phosphocholine

3-Benzylamino-1-O-dodecyl-propan-1.2-diol-2-O-phosphocholine

3-Benzylamino-1-O-tetradecyl-propan-1.2-diol-2-O-phosphocholine

3-Benzylamino-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-Benzylamino-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-Benzylamino-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-phenylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Octadecyl-3-phenylamino-propan-1.2-diol-2-O-phosphocholine

3-Acetylamino-1-O-decyl-propan-1.2-diol-2-O-phosphocholine

3-Acetylamino-1-O-dodecyl-propan-1.2-diol-2-O-phosphocholine

3-Acetylamino-1-O-tetradecyl-propan-1.2-diol-2-O-phosphocholine

3-Acetylamino-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-Acetylamino-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-Acetylamino-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

3-Butyrylamino-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-Butyrylamino-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-Butyrylamino-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-palmitoylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Octadecyl-3-palmitoylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-palmitoylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-stearoylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Octadecyl-3-stearoylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-stearoylamino-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-methoxycarbonylamino-propan-1.2-diol-2-O-phosphocholine

3-Methoxycarbonylamino-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-methoxycarbonylamino-propan-1.2-diol-2-O-phosphocholine

3-Ethoxycarbonylamino-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-Ethoxycarbonylamino-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-ethoxycarbonylamino-propan-1.2-diol-2-O-phosphocholine

3-Benzyloxycarbonylamino-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-Benzyloxycarbonylamino-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-Benzyloxycarbonylamino-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-ureido-propan-1.2-diol-2-O-phosphocholine

1-O-Octadecyl-3-ureido-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-ureido-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-(3-methylureido)-propan-1.2-diol-2-O-phosphocholine

3-(3-Methylureido)-1-O-octadecyl-propan-1,2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(3-methylureido)-propan-1,2-diol-2-O-phosphocholine

3-(3-Ethylureido)-1-O-hexadecyl-propan-1,2-diol-2-O-phosphocholine

3-(3-Ethylureido)-1-O-octadecyl-propan-1,2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(3-ethylureido)-propan-1,2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-(3-hexadecylureido)-propan-1,2-diol-2-O-phosphocholine

3-(3-Hexadecylureido)-1-O-octadecyl-propan-1,2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(3-hexadecylureido)-propan-1,2-diol-2-O-phosphocholine

3-(3,3-Dimethylureido)-1-O-hexadecyl-propan-1,2-diol-2-O-phosphocholine

3-(3,3-Dimethylureido)-1-O-octadecyl-propan-1,2-diol-2-O-phosphocholine

3-(3,3-Dimethylureido)-1-O-eicosyl-propan-1,2-diol-2-O-phosphocholine

3-(3-Benzylureido)-1-O-hexadecyl-propan-1,2-diol-2-O-phosphocholine

3-(3-Benzylureido)-1-O-octadecyl-propan-1,2-diol-2-O-phosphocholine

3-(3-Benzylureido)-1-O-eicosyl-propan-1,2-diol-2-O-phosphocholine

3-(N-Acetyl-methylamino)-1-O-hexadecyl-propan-1,2-diol-2-O-phosphocholine

3-(N-Acetyl-methylamino)-1-O-octadecyl-propan-1,2-diol-2-O-phosphocholine

3-(N-Acetyl-methylamino)-1-O-eicosyl-propan-1,2-diol-2-O-phosphocholine

3-(N-Acetyl-methylamino)-1-O-oleyl-propan-1,2-diol-2-O-phosphocholine

3-(N-Acetyl-methylamino)-1-O-linolyl-propan-1,2-diol-2-O-phosphocholine

3-(N-Benzoyl-methylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholin

3-(N-Benzoyl-methylamino)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholin

3-(N-Benzoyl-methylamino)-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzoyl-methylamino)-1-O-oleyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzoyl-methylamino)-1-O-linolyl-propan-1.2-diol-2-O-phosphocholine

3-[N-(4-Chlorobenzoyl)-methylamino]-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-[N-(4-methoxybenzoyl)-methylamino]-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-[N-(4-methylbenzoyl)-methylamino]-propan-1.2-diol-2-O-phosphocholine

3-[N-(4-Ethoxybenzoyl)-methylamino]-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-[N-(3-trifluormethylbenzoyl)-methylamino]-propan-1.2-diol-2-O-phosphocholine

3-(N-Acetyl-hexadecylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Acetyl-hexadecylamino)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Acetyl-hexadecylamino)-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Acetyl-benzylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Acetyl-benzylamino)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Acetyl-benzylamino)-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-(N-methyl-palmitoylamino)-propan-1.2-diol-2-O-phosphocholine

3-(N-Methyl-palmitoylamino)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(N-methyl-palmitoylamino)-propan-1.2-diol-2-O-phosphocholine

3-(N-Methyl-palmitoylamino)-1-O-oleyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Methyl-oleoylamino)-1-O-oleyl-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-(N-octadecyl-oleoylamino)-propan-1.2-diol-2-O-phosphocholine

3-(N-Ethoxycarbonyl-methylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Ethoxycarbonyl-methylamino)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(N-ethoxycarbonyl-methylamino)-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-methylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-methylamino)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-methylamino)-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-hexadecylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-hexadecylamino)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-hexadecylamino)-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-octadecylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-octadecylamino)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-octadecylamino)-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-eicosylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-eicosylamino)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyloxycarbonyl-eicosylamino)-1-O-eicosyl-propan-1 2-diol-2-O-phosphocholine

3-(N-Benzyl-benzyloxycarbonylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyl-benzyloxycarbonylamino)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyl-benzyloxycarbonylamino)-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Benzyl-benzyloxycarbonylamino)-1-O-oleyl-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-(1-methylureido)-propan-1.2-diol-2-O-phosphocholine

3-(1-Methylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(1-methylureido)-propan-1.2-diol-2-O-phosphocholine

3-(1-Ethylureido)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(1-Ethylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(1-ethylureido)-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-(1-hexadecylureido)-propan-1.2-diol-2-O-phosphocholine

3-(1-Hexadecylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(1-hexadecylureido)-propan-1.2-diol-2-O-phosphocholine

3-(1,3-Dimethylureido)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(1,3-Dimethylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-(1,3-Dimethylureido)-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

3-(1-Benzylureido)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(1-Benzylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-(1-Benzylureido)-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-(1-hexadecyl-3-methylureido)-propan-1.2-diol-2-O-phosphocholine

3-(1-Hexadecyl-3-methylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(1-hexadecyl-3-methylureido)-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-(3-methyl-1-octadecylureido)-propan-1.2-diol-2-O-phosphocholine

3-(3-Methyl-1-octadecylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(3-methyl-1-octadecylureido)-propan-1.2-diol-2-O-phosphocholine

3-(3-Ethyl-1-hexadecylureido)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(3-Ethyl-1-hexadecylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(3-ethyl-1-hexadecylureido)-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-(1-hexadecyl-3-phenylureido)-propan-1.2-diol-2-O-phosphocholine

3-[3-(4-chlorophenyl)-1-hexadecylureido]-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(1-Hexadecyl-3-phenylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(1-hexadecyl-3-phenylureido)-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-(3-phenylureido)-propan-1.2-diol-2-O-phosphocholine

1-O-Octadecyl-3-(3-phenylureido)-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(3-phenylureido)-propan-1.2-diol-2-O-phosphocholine

3-[3-(4-chlorophenyl)-ureido]-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-[3-(4-chlorophenyl)-ureido]-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-[3-(4-chlorophenyl)-ureido]-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-[3-(2-phenylethyl)-ureido]-propan-1.2-diol-2-O-phosphocholine

1-O-Octadecyl-3-[3-(2-phenylethyl)-ureido]-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-[3-(2-phenylethyl)-ureido]-propan-1.2-diol-2-O-phosphocholine

1-O-Hexadecyl-3-(2-phenylethylamino)-propan-1.2-diol-2-O-phosphocholine

1-O-Octadecyl-3-(2-phenylethylamino)-propan-1.2-diol-2-O-phosphocholine

1-O-Eicosyl-3-(2-phenylethylamino)-propan-1.2-diol-2-O-phosphocholine

3-(N-Acetyl-2-phenylethylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Acetyl-2-phenylethylamino)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Acetyl-2-phenylethylamino)-1-O-eicosyl-propan-1.2-diol-2-O-phosphocholine

3-(N-Acetyl-2-phenylethylamino)-1-O-oleyl-propan-1.2-diol-2-O-phosphocholine

[1-(N-Acetyl-aminomethyl)-2-hexadecyloxy-ethyl]-3-trimethyl-ammoniopropyl-phospate

[1-(N-Acetyl-aminomethyl)-2-hexadecyloxy-ethyl]-4-trimethyl-ammoniobutyl-phosphate

[1-(N-Acetyl-methylaminomethyl)-2-hexadecyloxy-ethyl]-3-trimethylammoniopropyl-phosphate

[1-(N-Acetyl-methylaminomethyl)-2-hexadecyloxy-ethyl]-4-trimethylammoniobutyl-phosphate

[1-(N-Acetyl-aminomethyl)-2-octadecyloxy-ethyl]-3-trimethyl-ammoniopropyl-phosphate

[1-(N-Acetyl-aminomethyl)-2-octadecyloxy-ethyl]-4-trimethylammoniobutyl-phosphate

[1-(N-Acetyl-methylaminomethyl)-2-octadecyloxy-ethyl]-3-trimethylammoniopropyl-phosphate

/1-(N-Acetyl-methylaminomethyl)-2-octadecyloxy-ethyl/-4-trimethylammoniobutyl-phosphate

/1-(N-Acetyl-aminomethyl)-2-hexadecyloxy-ethyl/-2-dimethylammonioethyl-phosphate

/1-(N-Acetyl-methylaminomethyl)-2-hexadecyloxy-ethyl/-2-dimethylammonioethyl-phosphate

/1-(N-Acetyl-aminomethyl)-2-octadecyloxy-ethyl/-2-dimethylammonioethyl-phosphate

/1-(N-Acetyl-methylaminomethyl)-2-octadecyloxy-ethyl/-2-dimethylammonioethyl-phosphate

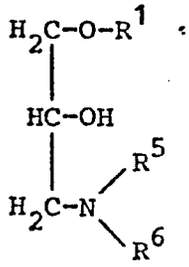
/1-(N-Acetyl-aminomethyl)-2-hexadecyloxy-ethyl/-2-butyldimethylammonioethyl-phosphate

/1-(N-Acetyl-aminomethyl)-2-octadecyloxy-ethyl/-2-butyldimethylammonioethyl-phosphate.

Depending upon the fact whether there has been effected a split of racemates, the above compounds may be present in their R- or S-form or as racemate mixture.

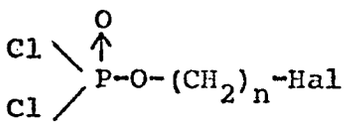
The compounds of the present invention are biologically very active and may be used for instance in drugs or in plant protection. Thus, they may be used for the treatment of high blood pressure, and for the therapy of cancer.

For preparing the new 1-O-alkyl-3-amino-propane-1.2-diol-2-O-phospholipids, 2.3-epoxypropylethers of formula $R^1-OCH_2-CH(O)-CH_2$ (regarding their production see E. Mouzin et al., Synthesis 1983, 117 and following) are subjected to reaction with the corresponding amine of formula $HN\begin{matrix}R^5\\R^6\end{matrix}$ corresponding to the procedure as known for epoxides (see for instance Houben-Weyl, Methoden der organischen Chemie, 4. Ed., Vol. 11/1, p. 314 and following, Georg Thieme Verlag, Stuttgart 1957) to yield the corresponding substituted 3-amino-2-hydroxy-propylethers and, if desired, to subject them to N-acylation by usual methods. The starting materials II



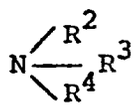
II

wherein R^1, R^5 and R^6 have the same meaning as in formula I, resulting therefrom are subjected to reaction with dichlorophosphoric acid-ω-halogene alkyl esters of formula III



III

wherein n has the same meaning as in formula I and Hal is a chlorine or bromine atom,
in an inert organic solvent, possibly with the addition of an auxiliary base such as pyridine or triethylamine, the resulting compounds subsequently being reacted with an amine of formula IV



IV

wherein R^2, R^3 and R^4 have the same meaning as in formula I in an inert organic solvent such as toluene, dioxane, tetrahydrofurane, possibly with the application of pressure (regarding thereto, see: H.K. Mangold, Angew. Chemie 91, 55o to 56o (1979; H. Eibl, Chem. and Phys. of Lipids 26, 4o5 to 429 (198o)).

If the resulting compounds of formula I have benzyl, benzyloxycarbonyl or similar protective groups, these groups may be split-off by hydrogenation under usual conditions in the presence of heavy metal catalysts and hydrogen, thus forming compounds of formula I wherein R^5 and/or R^6 is hydrogen.

On the other side, a compound of formula I wherein R^5 and/or R^6 is hydrogen may be subjected to reaction, in the presence of a suitable condensation agent such as thionylchloride, carbonylbisimidazol, carbodiimides and the like, with an acid of formula V

$$HOOC-(CH_2)_m-R^7 \qquad V$$

wherein m and R^7 have the same meaning as in formula I, or, possibly in the presence of auxiliary basis such as triethylamine, pyridine and the like, with an acid derivative of formula VI

$$Hal-A-(CH_2)_m-R^7 \qquad VI$$

wherein A, m and R^7 have the same meaning as in formula I (with the exception of A representing a bond) and Hal is a halogen atom or an acid anhydride group, in particular a chloro or a bromo atom. Acylation may also be effected with isocyanates of formula VII

$$R^5-N=C=O \qquad VII$$

wherein R^5 has the same meaning as in formula I, possibly with the addition of catalysts such as dimethylformamide or 4-dimethylaminopyridine.

The starting compounds of formula II may be used in their R- or S-form or as racemate; accordingly, there are obtained the R- or S-forms or racemate mixtures of the final products I.

The present invention is further related to pharmaceutical preparations which contain the 1-O-alkyl-3-amino-propan-1.2-diol-2-O-phospholipids of formula I. The pharmaceutical preparations according to the present invention are products for enteral as oral or rectal as well as parenteral application. They contain the pharmaceutically active agents

alone or together with usual, pharmaceutically applicable carrier materials. Preferably, the pharmaceutical preparations of the active agent are in the form of single doses corresponding to the desired form of application such as tablets, dragees, capsules, suppositories, granulates, solutions, emulsions or suspensions. The dosages of the compounds usually are between 1 and 1ooo mg. per day, preferably between 1o and 1oo mg. per day, and the product may be administered once or several times, preferably between two and three times, per day.

The preparation of the compounds according to the present invention are further illustrated by the following examples. The reported melting points have been determined by means of a Büchi 51o melting point apparatus and they are not corrected. The infrared spektra have been determined in a Perkin-Elmer 257 or Nicolet NIC-3600 type apparatus.

Example 1

3-(N-acetyl-methylamino)-1-O-hexadecyl-propan -1.2-diol-2-O-phosphocholine.

a) 1-Hexadecyloxy-3-methylamino-propan-2-ol.

A cooled mixture of 15.5 g of methylamine, 5o cc. of tetrahydrofurane and 15 g of hexadecyl-2.3-epoxypropylether is heated to 6o°C. for 2 hours in an autoclave, cooled and evaporated in a vacuo. The residue is purified by column chromatography (silicic acid gel//chloroform/methanol).

Yield: 1o.5 g F.: 89 to 91°C.

b) 3-(N-acetyl-methylamino)-1-hexadecyloxy-propan-2-ol.

5 g of 1-hexadecyloxy-3-methylamino-propan-2-ol are dissolved in 3o cc. of anhydrous chloroform. At first 3 g of triethylamine and separately thereafter 2.4 g of acetylchloride are added dropwise with cooling and the mixture is stirred for 8 hours. The chloroform solution

is washed with 2 % hydrochloric acid and water, is evaporated and the residue is dissolved in 1oo cc. of methanol. A solution of o.6 g of sodium hydroxide in a little methanol is added to the methanol solution and the mixture is stirred at room temperature for one hour. The solvent is evaporated in a vacuo and the residue is triturated in chloroform. The chloroform solution is washed with 2 % hydrochloric acid and water, is dried over sodium sulfate and is evaporated.

Yield: 3.7 g of an oil

IR (film): 335o, 163o 112o cm^{-1}.

c) [1-(N-acetyl-methylaminomethyl)-2-hexadecyloxyethyl]-2-bromoethyl phosphate.

3.3 g of 3-(N-acetyl-methylamino)-1-hexadecyloxy-propan-2-ol are dissolved in 1oo cc. of anhydrous chloroform and the solution is added dropwise to a mixture of 4.3 g of 2-bromoethylphosphoric acid dichloride, 1o cc. of chloroform and 5o cc. of pyridin cooled with ice. The resulting mixture is stirred for one hour at room tmperature, diluted with water and stirred another hour at room temperature. The organic phase is separated, washed with 5 % hydrochloric acid and water, dried over sodium sulfate and the solvent is separated in a vacuo. The residue is purified by column chromatography (silicic acid gel//chloroform/methanol).

Yield: 1.6 g of an oil.

d) 3-(N-acetyl-methylamino)-1-O-hexadecyl-propan -1.2-diol-2-O-phosphocholine.

1.6 g of [1-(N-acetyl-methylaminomethyl)-2-hexadecyloxyethyl]-2-bromoethyl phosphate are dissolved in 3o cc. of anhydrous toluene. About 3 cc. of a 33 % solution of trimethylamine in ethanol is added thereto and the resulting mixture is stirred for 4 hours at 6o°C. in a closed container. The solvent is evaporated in a vacuo and the residue is purified by column chromatography (silicic

acid gel//chloroform/methanol).

Yield: o.4 g of a waxy product
IR (film): 1635 cm^{-1}.

Example 2

3-(N-benzyl-benzyloxycarbonylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine.

a) 3-Benzylamino-1-hexadecyloxy-propan-2-ol.

A mixture of 24.4 g of benzylamine, 1oo cc. of tetrahydrofurane and 34 g of hexadecyl-2.3-epoxypropylether is refluxed for 8 hours and the solvent is evaporated in a vacuo. The residue is recrystallized from hexane.

Yield: 3o.8 g F.: 56 to 58°C.

b) 3-(N-benzyl-benzyloxycarbonylamino)-1-hexadecyloxy-propan-2-ol.

21.4 g of 3-benzylamino-1-hexadecyloxy-propan-2-ol are dissolved in 1oo cc. of anhydrous chloroform. At first 5.4 g of triethylamine and then a solution of 9 g of chloroformic acid benzyl ester in 5o cc. of chloroform is added dropwise with cooling and the mixture is stirred for 3 hours. The chloroform solution is washed with 5 % hydrochloric acid and water, dried over sodium sulfate, evaporated and the residue is purified by column chromatography (silicic acid gel//chloroform).

Yield: 21 g (oil)
IR (film): 3445, 17o1, 1125 cm^{-1}.

c) [1-(N-benzyl-benzyloxycarbonylaminomethyl)-2-hexadecyloxy-ethyl]-2-bromoethyl phosphate.

16 g of 3-(N-benzyl-benzyloxycarbonylamino)-1-hexadecyloxy-propan-2-ol are dissolved in 30 cc. of anhydrous chloroform and the solution is added dropwise to an ice-cooled mixture of 14.5 g of 2-bromoethylphosphoric acid dichloride, 120 cc. of chloroform and 9.5 g of pyridine. The mixture is stirred for 1 hour at room temperature, diluted with water and again stirred for 1 hour at room temperature. The organic phase is separated, washed with 5 % hydrochloric acid and water, dried over sodium sulfate and the solvent is evaporated in a vacuo. The residue is purified by column chromatography (silicic acid gel// chloroform/methanol).

Yield: 11.8 g (oil).

d) 3-(N-benzyl-benzyloxycarbonylamino)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine.

11.5 g of [1-(N-benzyl-benzyloxycarbonylaminomethyl)-2-hexadecyloxyethyl]-2-bromoethylphosphate are dissolved in 50 cc. of anhydrous toluene. About 10 cc. of a 33 % solution of trimethylamine in ethanol is added thereto and the mixture is stirred for 4 hours at 60°C. in a closed container. The solvent is evaporated in a vacuo and the residue is purified by column chromatography (silicic acid gel//chloroform/methanol).

Yield: 4.6 g of a waxy product

IR (film): 1696 cm^{-1}.

Example 3

3-Amino-1-O-hexadecyl-propan -1.2-diol-2-O-phosphocholine.

4.3 g of 3-(N-benzylbenzyloxycarbonylamino)-1-O-hexadecyl-propan -1.2-diol-2-O-phosphocholine are dissolved in 2oo cc. of a 4:1 (v/v)-mixture of dioxane and water and, after the addition of o.43 g of palladium-active carbon, are hydrogenated with hydrogen. The solution is filtered, the filter residue is washed with ethanol, the filtrates are combined and evaporated to dryness. The residue is purified by column chromatography (silicic acid gel //chloroform/methanol/conc. ammonia).

Yield: 1.4 g F.: 217 to 219°C.

Example 4

3-Benzylamino-1-O-hexadecyl-propan -1.2-diol-2-O-phosphocholine as produced similarly to Example 3 by inclomplete hydrogenation.

For instance, there are isolated with the procedure described in Example 3 o.3 g of waxy 3-benzylamino-1-O-hexadecyl-propan -1.2-diol-2-O-phosphocholine as side product. With the same procedure there of course may be also produced the 3-alkylamino-, 3-arylamino- and 3-arylalkylamino-compounds.

Example 5

3-Acetylamino-1-O-hexadecyl-propan -1.2-diol-2-O-phosphocholine.

a) o.35 g of 3-amino-1-O-hexadecyl-propan -1.2-diol-2-O-phosphocholine are dissolved in 1o cc. of anhydrous chloroform. 0.14 g of acetic acid anhydrideare added thereto and the mixture is stirred for about 12 hours at room temperature. The solution is evaporated in a vacuo and the residue is purified by column chromatography (silicic acid gel//chloroform/methanol/water).

Yield: o.2 g F.: 237 to 239°C.
IR (in KBr): 1667 cm^{-1}.

b) o.24 g of 3-amino-1-O-hexadecyl-propan -1.2-diol-2-O-phosphocholine are dissolved in 5 cc. of anhydrous chloroform. o.1 g of triethylamine and o.o8 g of acetylchloride are added thereto and the mixture is stirred for about 12 hours at room temperature. The solution is evaporated in a vacuo and the residue is purified by column chromatography (silicic acid gel//chloroform/methanol/water).

Yield: o.18 g

Example 6

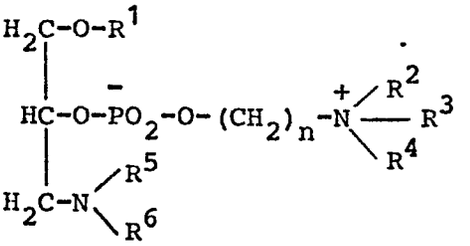
1-O-Hexadecyl-3-(3-methylureido)-propan -1.2-diol-2-O-phosphocholine.

o.48 g of 3-amino-1-O-hexadecyl-propan -1.2-diol-2-O-phosphocholine are dissolved in 1o cc. of anhydrous chloroform. o.17 g of methylisocyanate are added to this solution and the mixture is stirred for 12 hours at room temperature. The solution is evaporated in a vacuo and the residue is purified by column chromatography (Silicic acid gel//chloroform/methanol/water).

Yield: o.4 g F.: 243 to 245°C.

Patent claims

1. 1-O-Alkyl-3-amino-propan-1.2-diol-2-O-phospholipids and their derivatives of the formula I



I

wherein

R^1 is a saturated or unsaturated, straight-chain or branched alkyl group with 1o to 2o carbon atoms,

R^2, R^3 and R^4 which may be the same or different, represent hydrogen or a lower alkyl group with 1 to 4 carbon atoms,

R^5 and R^6 which may be the same or different, represent hydrogen or the group $-A-C_mH_{2m}-R^7$ or $-A-C_mH_{2m-2}-R^7$,

R^7 is hydrogen, unsubstituted phenyl or phenyl substituted by a C_{1-3}-alkyl, C_{1-3}-alkoxy, trifluoromethyl group, or a halogen atom,

A is a bond, -CO-, -COO- or $-CONR^8-$,

R^8 is hydrogen or C_{1-4}-alkyl,

m is a numeral from 0 to 2o and

n is a numeral from 2 to 4.

2. 1-O-Alkyl-3-amino-propan-1.2-diol-2-O-phospholipids of the general formula I according to claim 1 wherein

R^1 is a saturated or unsaturated, straight-chain alkyl group with 1o to 2o carbon atoms,

R^2, R^3 and R^4 which may be the same or different, represent hydrogen or methyl,

R^5 and R^6 which may be the same or different, represent hydrogen or the group $-A-(CH_2)_m-R^7$,

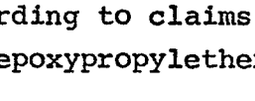
R^7 is hydrogen, unsubstituted phenyl or phenyl substituted by a methyl, methoxy, halogen, trifluoromethyl group,

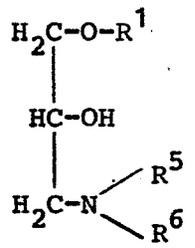
A is a bond, -CO-, -COO- or $-CONR^8-$,

R^8 is hydrogen or C_{1-4}-alkyl,

m is a numeral from 0 to 2o, if R^7 is hydrogen, or is a numeral from 0 to 2, if R^7 is phenyl or substituted phenyl and

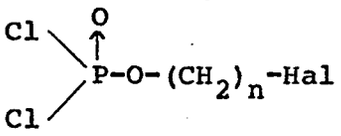
n is 2.

3. Process for producing the compounds of formula I according to claims 1 and 2 characterized in that 2.3-epoxypropylether of formula  wherein R^1 has the same meaning as in formula I, is subjected to reaction with an amine of formula  wherein R^5 and R^6 have the same meaning as in formula I, and possibly subsequent N-acylation to the starting compounds of the formula II



II

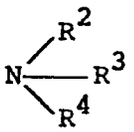
wherein R^1, R^5 and R^6 have the same meaning as in formula I, and subjecting the same to reaction with a dichlorophosphoric acid-ω-halogeno alkyl ester of formula III



III

wherein n has the same meaning as in formula I and Hal is a chlorine or bromine atom,

in an inert organic solvent, possibly with the use of an auxiliary base, and subsequent reaction with an amine of formula IV

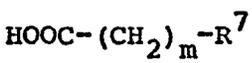


IV

wherein R^2, R^3 and R^4 have the same meaning as in formula I, in an inert organic solvent, possibly with the application of pressure.

4. Process for the preparation of compounds of formula I wherein R^5 and/or R^6 are hydrogen according to claims 1 or 2 characterized in that a compound of formula I wherein one or both of R^5 and/or R^6 represent a benzyl or benzyloxycarbonyl group, is subjected to hydration in an inert solvent in the presence of a usual catalyst for hydration.

5. Process for the production of compounds of formula I according to claims 1 or 2 characterized in that a compound of formula I with R^5 and/or R^6 are hydrogen, is subjected to reaction with an acid of formula V



V

wherein m and R^7 have the same meaning as in formula I, in the presence of suitable condensation agents or, possibly in the presence of auxiliary bases, with an acid derivative of formula VI

$$Hal\text{-}A\text{-}(CH_2)_m\text{-}R^7 \qquad VI$$

wherein A, m and R^7 have the same meaning as in formula I, except A representing a bond, and Hal is a halogen atom or an acid anhydride group, or, possibly with the addition of a Lewis-base as catalyst, is subjected to reaction with an isocyanate of formula VII

$$R^5\text{-}N{=}C{=}O \qquad VII$$

wherein R^5 has the same meaning as in formula I, at the 3-amino group.

6. Pharmaceutical preparations characterized in that they contain a compound of general formula I according to claims 1 and 2 as active agent mixed with usual pharmaceutical auxiliary and carrier agents.

European Patent Office

EUROPEAN SEARCH REPORT

Application number

EP 84 10 7293

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)
A	GB-A-2 020 663 (NATTERMANN)	1	C 07 F 9/10 A 61 K 31/685
A,P	EP-A-0 092 190 (FUJISAWA PHARMACEUTICAL)	1	

TECHNICAL FIELDS SEARCHED (Int. Cl. ³)

C 07 F 9/10

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
BERLIN	14-09-1984	KAPTEYN H G

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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