

United States Patent [19]

Lautenschläger et al.

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[54] 1-O-ALKYL-3-AMINO-PROPAN-1,2-DIOL-2-O-PHOSPHOLIPIDS

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[30] Foreign Application Priority Data

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[58] Field of Search 260/925

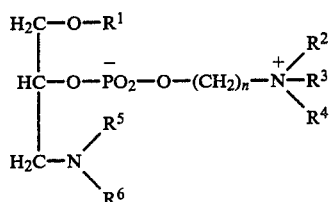
[56] References Cited
PUBLICATIONS

Synthesis, Feb. 1983, pp. 117 to 119.
H. K. Mangold, Angew. Chem. 91, 550, 554 (1979).
H. Eibl, Chemistry and Physics of Lipids, 26 (1980), pp. 405, 416.

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[57] ABSTRACT

The invention is related to 1-O-alkyl-3-amino-propan-1,2-diol-2-O-phospholipids having the formula I



2 Claims, No Drawings

- 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
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- 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
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- 3-(3-Methylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine
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- 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
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- 3-(3-Benzylureido)-1-O-hexadecyl-propan-1.2-diol-2-O-phosphocholine
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- 3-(N-Acetyl-methylamino)-1-O-oleyl-propan-1.2-diol-2-O-phosphocholine
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- 3-(N-Benzoyl-methylamino)-1-O-linolyl-propan-1.2-diol-2-O-phosphocholine
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1-O-Hexadecyl-3-[N-(4-methoxybenzoyl)-methylamino]-propan-1.2-diol-2-O-phosphocholine
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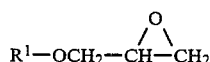
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 3-(1-Methylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine
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 3-(1-Hexadecylureido)-1-O-octadecyl-propan-1.2-diol-2-O-phosphocholine
 1-O-Eicosyl-3-(1-hexadecylureido)-propan-1.2-diol-2-O-phosphocholine
 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
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 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
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 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
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 1-O-Octadecyl-b 3-(3-phenylureido)-propan-1.2-diol-2-O-phosphocholine
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 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-trimethylammonioethyl-phosphate
 [1-(N-Acetyl-aminomethyl)-2-hexadecyloxy-ethyl]-4-trimethylammonioethyl-phosphate
 [1-(N-Acetyl-methylaminomethyl)-2-hexadecyloxy-ethyl]-3-trimethylammonioethyl-phosphate
 [1-(N-Acetyl-methylaminomethyl)-2-hexadecyloxy-ethyl]-4-trimethylammonioethyl-phosphate
 [1-(N-Acetyl-aminomethyl)-2-octadecyloxy-ethyl]-3-trimethylammonioethyl-phosphate
 [1-(N-Acetyl-aminomethyl)-2-octadecyloxy-ethyl]-4-trimethylammonioethyl-phosphate
 [1-(N-Acetyl-methylaminomethyl)-2-octadecyloxy-ethyl]-3-trimethylammonioethyl-phosphate
 [1-(N-Acetyl-methylaminomethyl)-2-octadecyloxy-ethyl]-4-trimethylammonioethyl-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. Thus, they may be used for the treatment of asthma.

For preparing the new 1-O-alkyl-3-amino-propane-1.2-diol-2-O-phospholipids, 2,3-epoxypropylethers of formula



(regarding their production see E. Mouzin et al., Synthesis 1983, 117 and following) are subjected to reaction with the corresponding amine of formula

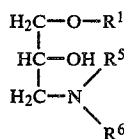


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corresponding to the procedure as known for epoxides (see for instance Houben-Weyl, Methoden der organischen Chemie, 4. Ed., Vol. 11/1, p. 314 and following, Georg Thieme Verlag, Stuttgart 1957) to yield the corresponding substituted 3-amino-2-hydroxy-propylethers and, if desired, to subject them to N-acylation by usual methods. The starting materials II

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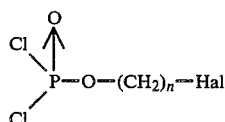


II

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wherein R¹, R⁵ and R⁶ have the same meaning as in formula I, resulting therefrom are subjected to reaction with dichlorophosphoric acid- ω -halogene alkyl esters of formula III

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III

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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

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IV

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wherein R², R³ and R⁴ have the same meaning as in formula I in an inert organic solvent such as toluene, dioxane, tetrahydrofuran, possibly with the application of pressure (regarding thereto, see: H. K. Mangold, Angew. Chemie 91, 550 to 560 (1979); H. Eibl, Chem. and Phys. of Lipids 26, 405 to 429 (1980)).

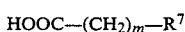
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If the resulting compounds of formula I have benzyl, benzyloxycarbonyl or similar protective groups, these groups may be split-off by hydrogenation under usual conditions in the presence of heavy metal catalysts and hydrogen, thus forming compounds of formula I wherein R⁵ and/or R⁶ is hydrogen.

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On the other side, a compound of formula I wherein R⁵ and/or R⁶ 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

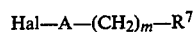
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V

wherein m and R⁷ 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



wherein A, m and R⁷ 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



wherein R⁵ 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 1000 mg. per day, preferably between 10 and 100 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 510 melting point apparatus and they are not corrected. The infrared spectra 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, 50 cc. of tetrahydrofuran and 15 g of hexadecyl-2,3-epoxypropylether is heated to 60° 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: 10.5 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 30 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 100 cc. of methanol. A solution of 0.6 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): 3350, 1630 1120 cm⁻¹.

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

3.3 g of 3-(N-acetyl-methylamino)-1-hexadecyloxypropan-2-ol are dissolved in 100 cc. of anhydrous chloroform and the solution is added dropwise to a mixture of 4.3 g of 2-bromoethylphosphoric acid dichloride, 10 cc. of chloroform and 50 cc. of pyridin cooled with ice. The resulting mixture is stirred for one hour at room temperature, 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 30 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 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: 0.4 g of a waxy product.

IR (film): 1635 cm⁻¹.

EXAMPLE 2

3-(N-benzyl-benzoyloxycarbonylamino)-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, 100 cc. of tetrahydrofuran 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: 30.8 g. F.: 56° to 58° C.

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

21.4 g of 3-benzylamino-1-hexadecyloxy-propan-2-ol are dissolved in 100 cc. of anhydrous chloroform. At first 5.4 g of triethylamine and then a solution of 9 g of chloroformic acid benzyl ester in 50 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, 1701, 1125 cm⁻¹.

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

16 g of 3-(N-benzyl-benzoyloxycarbonylamino)-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 sepa-

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R⁷ is a member selected from the group consisting of hydrogen, unsubstituted phenyl and phenyl substituted by a methyl, a methoxy, a trifluoromethyl group or a halogen atom,

A is a member selected from the group consisting of a bond, and the groups —CO—, —COO— and —CONR⁸—,

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R⁸ is a member selected from the group consisting of hydrogen and C₁₋₄-alkyl,

m is a numeral from 0 to 20, if R⁷ is hydrogen, or is a numeral from 0 to 2, if R⁷ is unsubstituted or substituted phenyl and

n is 2.

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