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71 Applicant: **A. Nattermann & Cie. GmbH**
Nattermannallee 1
D-5000 Köln 30(DE)

72 Inventor: **Lautenschläger, Hans-Heiner, Dr.**
Neusser Gasse 50
D-5024 Pulheim(DE)

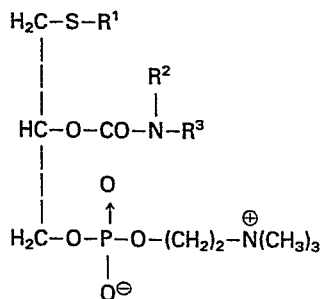
72 Inventor: **Betzing, Hans, Dr.**
Heidestock 7
D-5014 Kerpen(DE)

72 Inventor: **Winkelmann, Johannes, Dr.**
Frankfurter Strasse 269
D-5000 Köln 90(DE)

74 Representative: **Redies, Bernd, Dr. rer. nat. et al.**
Redies, Redies, Türk & Gille Brucknerstrasse 20
D-4000 Düsseldorf 13(DE)

54 **New 3-alkylthio-2-O-carbamoyl-propane-1,2-diol-1-O-phosphocholines, and processes for their preparation.**

57 The present invention relates to new 3-alkylthio-2-O-carbamoyl-propan-1,2-diol-1-O-phosphocholines of the general formula I

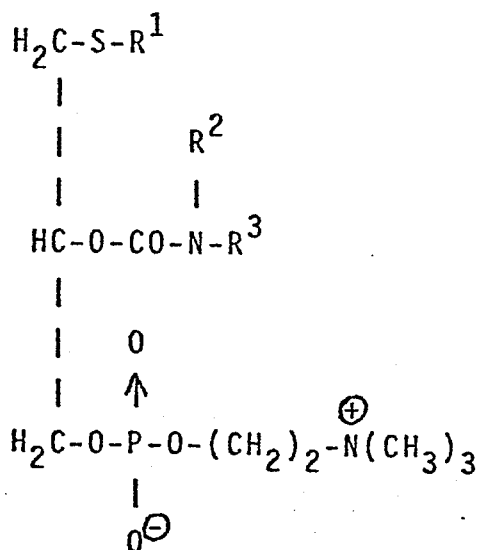


and processes for their preparation.

The present invention is related to new 3-alkylthio-2-O-carbamoyl-propan-1,2-diol-1-O-phosphocholines and processes for their preparation.

The compounds of the invention correspond to the general formula I

05



I

wherein R^1 signifies a straight chain saturated or unsaturated hydrocarbon residue with 10 to 20 carbon atoms, while R^2 and R^3 can be the same or different and signify a straight or branched chain, saturated or unsaturated hydrocarbon residue with 1 to 20 carbon atoms, phenyl, phenyl mono-substituted by C_{1-3} alkyl, C_{1-3} alkoxy, halogen or trifluoromethyl, or signify benzyl or hydrogen.

10

Compounds of the invention are for example:

- 3-Hexadecylthio-2-0-methylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 2-0-ethylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 05 3-hexadecylthio-2-0-propylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-isopropylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 10 2-0-butylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-pentylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-hexylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 15 2-0-methylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-ethylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 20 3-octadecylthio-2-0-propylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 2-0-isopropylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-butylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 25 3-octadecylthio-2-0-pentylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 2-0-hexylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 30 2-0-methylcarbamoyl-3-oleylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-ethylcarbamoyl-3-linoleylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-dimethylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 35 1-0-phosphocholine,

- 2-0-dimethylcarbamoyl-3-hexadecylthio-propan-1.2-diol-
1-0-phosphocholine,
2-0-decylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-
0-phosphocholine,
05 3-hexadecylthio-2-0-undecylcarbamoyl-propan-1.2-diol-
1-0-phosphocholine,
2-0-dodecylcarbamoyl-3-hexadecylthio-propan-1.2-diol-
1-0-phosphocholine,
3-hexadecylthio-2-0-tetradecylcarbamoyl-propan-1.2-diol-
10 1-0-phosphocholine,
2-0-hexadecylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-
phosphocholine,
3-hexadecylthio-2-0-octadecylcarbamoyl-propan-1.2-diol-1-0-
phosphocholine,
15 2-0-eicosylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-
phosphocholine,
2-0-decylcarbamoyl-3-octadecylthio-propan-1,2-diol-1-0-
phosphocholine,
3-octadecylthio-2-0-undecylcarbamoyl-propan-1.2-diol-1-0-
20 phosphocholine,
2-0-dodecylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-
phosphocholine,
3-octadecylthio-2-0-tetradecylcarbamoyl-propan-1,2-diol-1-
0-phosphocholine,
25 2-0-hexadecylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-
phosphocholine,
2-0-octadecylcarbamoyl-3-octadecylthio-propan-1,2-diol-1-0-
phosphocholine,
2-0-eicosylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-
30 phosphocholine,
3-hexadecylthio-2-0-phenylcarbamoyl-propan-1,2-diol-1-0-
phosphocholine,
2-0-(2-fluorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-
diol-1-0-phosphocholine,
35 2-0-(3-fluorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-
diol-1-0-phosphocholine,

- 2-0-(4-fluorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-(2-chlorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 05 2-0-(3-chlorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-(4-chlorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-(4-bromophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 10 3-hexadecylthio-2-0-(2-methylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-(3-methylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 15 3-hexadecylthio-2-0-(4-methylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-(2-methoxyphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-(4-methoxyphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 20 2-0-(2-ethoxyphenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-(4-ethoxyphenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 25 3-hexadecylthio-2-0-(2-trifluoromethylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-(3-trifluoromethylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 3-oleylthio-2-0-phenylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 30 3-linoleylthio-2-0-phenylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 3-octadecylthio-2-0-phenylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 35 2-0-(2-fluorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,

- 2-0-(3-fluorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-(4-fluorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 05 2-0-(2-chlorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-(3-chlorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 10 2-0-(4-chlorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-(4-bromophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-(2-methylphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 15 2-0-(3-methylphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-(4-methylphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 20 2-0-(2-methoxyphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-(4-methoxyphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-(2-ethoxyphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 25 2-0-(4-ethoxyphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 3-octadecylthio-2-0-(2-trifluoromethylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 3-octadecylthio-2-0-(3-trifluoromethylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 30 2-0-benzylcarbamoyl-3-octadecylthio-propan-1,2-diol-1-0-phosphocholine,
- 2-0-benzylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine.

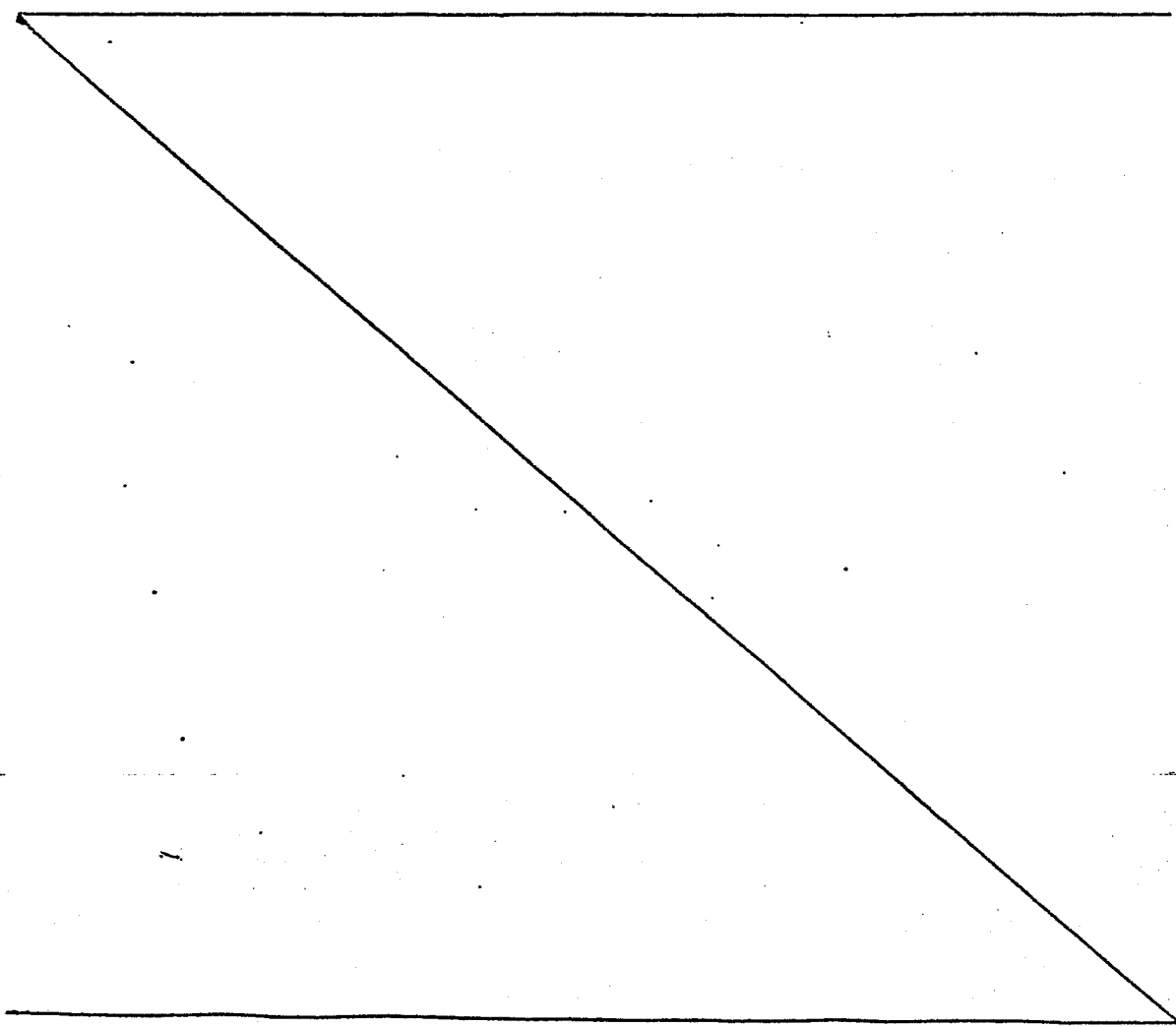
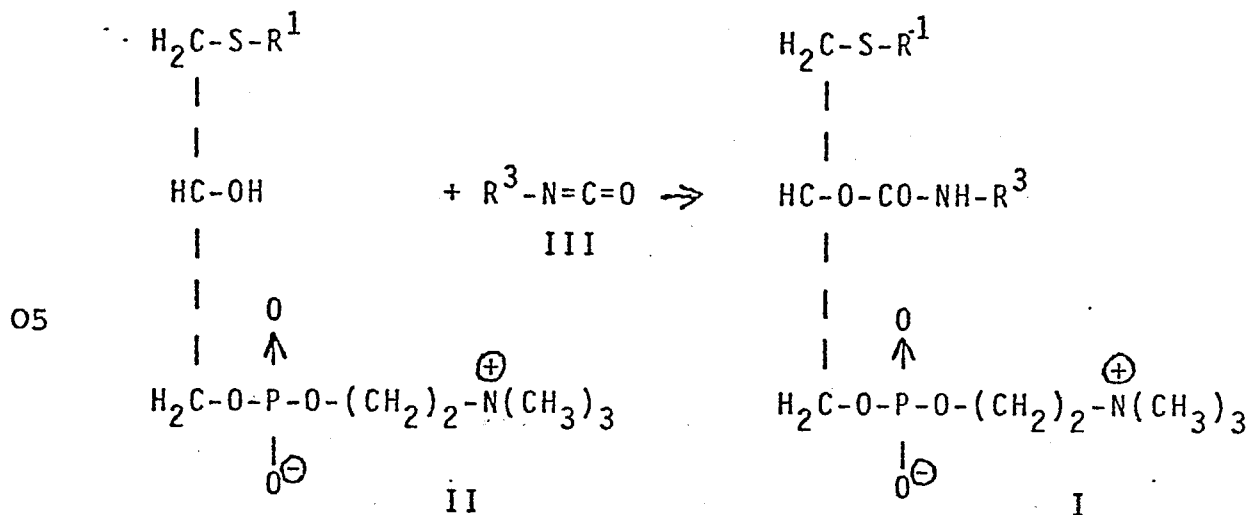
The compounds of the invention possess valuable pharmacological properties and are thus suitable for use as active ingredients in medicaments.

05 Of the substances of the invention listed, some, e.g.
3-hexadecylthio-2-O-methylcarbamoyl-propan-1.2-diol-1-O-
10 phosphocholine, or 2-O-ethylcarbamoyl-3-octadecylthio-
propan-1.2-diol-1-O-phosphocholine, are particularly
preferred. The said compounds can be used for the treatment
of high blood pressure, various rheumatic and some atheros-
clerotic conditions as well as for tumour therapy in humans.

15 The compounds of formula I are administered in the form of
pharmaceutical preparations for enteral, oral, rectal as
well as parenteral administration, and they contain the
pharmaceutical active ingredients alone or together with
a conventional pharmaceutically usable carrier material.
20 Advantageously the pharmaceutical presentation of the
active ingredient is in the form of single doses, which
are adapted to the desired mode of administration, e.g.
tablets, dragees, capsules, suppositories, granulates,
solutions, emulsions or suspensions. The dosage of the
compounds of formula I lies normally between 1 and 1000 mg.
per dose, preferably between 1 to 10 mg. per dose, and can
be administered once or oftener, preferably 2 to 3 times
daily.

25 Also preferred are compounds, e.g. 3-hexadecylthio-2-O-
hexadecylcarbamoyl-propan-1.2-diol-1-O-phosphocholine,
which possess clear advantages compared with the natural
or synthetic 1.2-diacyl-glycero-3-phosphocholines (e.g.
30 GB-PS 1,523,965) previously used in liposome technology,
since they in contrast to the latter phospholipids, are
resistant to phospholipase A₂ and thus permit better trans-
fer of the included active ingredient at the site of their
effect.

The invented substances of the formula I in which $R^2 = H$ are prepared by reaction of the lyso-compounds II, wherein R^1 has the meaning given in formula I, with the corresponding alkyl or aryl isocyanates of the formula III.



The reaction is usefully carried out in organic aprotic solvents e.g. chloroform, acetone, dimethylformamide or mixtures thereof, with optional use of a catalyst, especially a Lewis base, e.g. triethylamine, pyridine, dimethylaminopyridine, dimethylformamide, at temperatures between 0° and 100°C; preferably 40° to 60° C.

As starting compounds of the formula II there may be mentioned:

3-Decylthio-propan-1.2-diol-1-0-phosphocholine,
3-undecylthio-propan-1.2-diol-1-0-phosphocholine,
3-dodecylthio-propan-1.2-diol-1-0-phosphocholine,
3-tridecylthio-propan-1.2-diol-1-0-phosphocholine,
3-tetradecylthio-propan-1.2-diol-1-0-phosphocholine,
3-pentadecylthio-propan-1.2-diol-1-0-phosphocholine,
3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
3-heptadecylthio-propan-1.2-diol-1-0-phosphocholine,
3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
3-nonadecylthio-propan-1.2-diol-1-0-phosphocholine,
3-eicosylthio-propan-1.2-diol-1-0-phosphocholine,
3-oleylthio-propan-1.2-diol-1-0-phosphocholine,
3-linoleylthio-propan-1.2-diol-1-0-phosphocholine,
and the lyso-compounds can be used in their R- or S-form or as a racemic mixture.

As starting compounds of formula III there may be mentioned:

methyl isocyanate, ethyl isocyanate, propyl isocyanate, isopropyl isocyanate, allyl isocyanate, butyl isocyanate, pentyl isocyanate, hexyl isocyanate, decyl isocyanate, undecyl isocyanate, dodecyl isocyanate, tridecyl isocyanate, tetradecyl isocyanate, pentadecyl isocyanate, hexadecyl isocyanate, octadecyl isocyanate, nonadecyl isocyanate, eicosyl isocyanate, oleyl isocyanate, linoleyl isocyanate, phenyl isocyanate, 2-fluorophenyl isocyanate, 3-fluorophenyl isocyanate, 4-fluorophenyl isocyanate,

05 2-chlorophenyl isocyanate, 3-chlorophenyl isocyanate,
4-chlorophenyl isocyanate, 4-bromophenyl isocyanate,
2-methylphenyl isocyanate, 3-methylphenyl isocyanate,
4-methylphenyl isocyanate, 2-methoxyphenyl isocyanate,
4-methoxyphenyl isocyanate, 2-ethoxyphenyl isocyanate,
4-ethoxyphenyl isocyanate, 2-(trifluoromethyl)-phenyl
isocyanate, 3-(trifluoromethyl)-phenyl isocyanate, benzyl
isocyanate.

10 The 3-alkylthiopropyl-1,2-diol-1-O-phosphocholines of the
formula II used as starting compounds can be synthesized
from the corresponding 2-O-acyl-3-alkylthio-propyl-1,2-
diol-1-O-phosphocholines by conventional procedures, e.g.
by enzymatic splitting (Phospholipase A₂) or mild alkaline
hydrolysis.

15 The 3-alkylthio-2-O-dialkylcarbamoyl-propyl-1,2-diol-1-O-
phosphocholines of the formula I can be synthesized from
the said lyso-compounds II by reaction with dialkyl
carbamic acid halides, especially with chlorides of the
formula IV

20



such as
25 N,N-dimethylcarbamic acid chloride, N-ethyl-N-methyl-
carbamic acid chloride, N,N-diethylcarbamic acid chloride,
N-methyl-N-propylcarbamic acid chloride, N,N-dipropyl-
carbamic acid chloride, in inert organic solvents, e.g.
chloroform, as well as solvent mixtures, with optional
addition of conventional bases, e.g. tertiary amines, metal
30 oxides, metal carbonates. The preparation of the compounds
of the invention is described in greater detail by the
following examples. The melting points were measured with

a Buechi 510 melting point determination apparatus and are uncorrected.

Example 1

05 3-Hexadecylthio-2-O-methylcarbamoyl-propan-1,2-diol-1-O-phosphocholine.

a) β -Bromoethyl-(3-hexadecylthio-2-hydroxypropyl)-phosphate.

A mixture of 30 g of hexadecylthio-propan-1,2-diol and 300 ml of dry chloroform is cooled to 0°C and a solution of 21.6 g of β -bromoethylphosphoric acid dichloride in 25 ml of chloroform and a solution of 7.2 ml of pyridine in 25 ml of chloroform are simultaneously and slowly added dropwise to the mixture with stirring. After half an hour of further stirring another 7.2 ml of pyridine is added and the mixture is stirred for 12 hours at room temperature and, following addition of ice water, stirred for a further hour. The organic phase is separated, washed neutral with water and sodium chloride solution, dried over sodium sulfate and evaporated in vacuo. The residue is purified by column chromatography (silica gel//chloroform/methanol).

20 Yield: 11.9 g. Mp: 197 to 198°C.

b) β -Bromoethyl-(2-acetyloxy-3-hexadecylthiopropyl)-phosphate.

14.6 g of β -bromoethyl-(3-hexadecylthio-2-hydroxy-propyl)-phosphate is dissolved in 100 ml of dry chloroform and the solution is treated with 7 ml of pyridine and 8.2 ml of acetic anhydride. After stirring at room temperature for 48 hours a little water is added and stirring continued for 15 minutes. The mixture is evaporated in vacuo and the residue is purified by column chromatography (silica gel//chloroform/methanol).

30 Yield: 5.1 g. Mp: >63°C.

c) 2-O-Acetyl-3-hexadecylthio-propan-1.2-diol-1-O-phosphocholine.

05 1.8 g of β -bromoethyl-(2-acetyloxy-3-hexadecylthiopropyl)-phosphate is dissolved in 3 ml of toluene, the solution is treated with 3 ml of a 20 % solution of trimethylamine in toluene and stirred for 3 hours at 60°C in a closed vessel. The reaction mixture is evaporated in vacuo and the residue purified by column chromatography (silica gel//chloroform/methanol/water = 80/20/2, 40/20/2, 20/20/2 (V/V/V)).

10 Yield: 0.9 g. Mp: 246 to 249°C (dec).

d) 3-Hexadecylthio-propan-1.2-diol-1-O-phosphocholine.

0.8 g of 2-O-acetyl-3-hexadecylthio-propan-1.2-diol-1-O-phosphocholine are dissolved in 15 ml of ethanol and 0.2 g of powdered potassium carbonate is added. After stirring for 15 48 hours, the salts are filtered off and washed with chloroform, the combined filtrates evaporated in vacuo and the residue purified by column chromatography (silica gel//chloroform/methanol/water = 80/20/2, 60/20/2, 50/20/2, 40/20/2, 30/20/2, 20/20/2 (V/V/V)).

20 Yield: 0.4 g. Mp: 252 to 254°C.

e) 3-Hexadecylthio-2-O-methylcarbamoyl-propan-1.2-diol-1-O-phosphocholine.

0.17 g of 3-hexadecylthio-propan-1.2-diol-1-O-phosphocholine is dissolved in 10 ml of dry chloroform and 1 ml of 25 dimethyl formamide, and 2 ml of methyl isocyanate is added. After stirring for 48 hours at 40°C, the solution is evaporated in vacuo and the residue purified by column chromatography (silica gel//chloroform/methanol/water = 80/20/2, 60/20/2, 40/20/2, 20/20/2 (V/V/V)).

30 Yield: 0.14 g. Mp. 252 to 254°C.

Example 2

2-0-Ethylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine.

05 0.17 g of 3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine are dissolved in 10 ml of dry chloroform, and 1 ml of dimethylformamide and 1 ml of ethyl isocyanate is added. After stirring for 48 hours at 40°C, the solution is evaporated in vacuo and the residue purified by column chromatography (silica gel//chloroform/methanol/water = 10 80/20/2, 60/20/2, 40/20/2, 20/20/2 (V/V/V)). Yield: 0.15 g. Mp: 250 to 252°C.

The following are prepared in a manner similar to examples 1 and 2:

- 15 3-Hexadecylthio-2-0-propylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-isopropylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 2-0-butylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 20 3-hexadecylthio-2-0-pentylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-hexylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 25 2-0-methylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-ethylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 3-octadecylthio-2-0-propylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 30 2-0-isopropylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-butylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 35 3-octadecylthio-2-0-pentylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,

- 2-0-hexylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
3-linoleylthio-2-0-methylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
05 2-0-ethylcarbamoyl-3-linoleylthio-propan-1.2-diol-1-0-phosphocholine,
3-linoleylthio-2-0-propylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
2-0-butylcarbamoyl-3-linoleylthio-propan-1.2-diol-1-0-phosphocholine,
10 3-linoleylthio-2-0-pentylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
2-0-hexylcarbamoyl-3-linoleylthio-propan-1.2-diol-1-0-phosphocholine,
15 2-0-methylcarbamoyl-3-oleylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-ethylcarbamoyl-3-oleylthio-propan-1.2-diol-1-0-phosphocholine,
3-oleylthio-2-0-propylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
20 2-0-butylcarbamoyl-3-oleylthio-propan-1.2-diol-1-0-phosphocholine,
3-oleylthio-2-0-pentylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
25 2-0-hexylcarbamoyl-3-oleylthio-propan-1.2-diol-1-0-phosphocholine.

Example 3

2-0-Hexadecylcarbamoyl-1-hexadecylthio-propan-1.2-diol-1-0-phosphocholine.

- 30 A mixture of 100 mg of 2-0-hexadecylcarbamoyl-1-hexadecylthio-propan-1.2-diol-1-0-phosphocholine, 200 mg. of hexadecyl isocyanate, 10 ml of chloroform and 1 ml of dimethylformamide is stirred at 60°C (48 hours). The excess alkyl isocyanate is hydrolyzed by addition of a little water and
35 the mixture is substantially evaporated in vacuo. The

residue is purified by column chromatography (silica gel//chloroform/methanol/water).

Yield: 93 mg. Mp: 220 to 225°C.

The following are prepared by analogous methods:

- 3-Hexadecylthio-2-0-octadecylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 2-0-hexadecylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 3-octadecylthio-2-0-octadecylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 2-0-decylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-undecylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 2-0-dodecylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-tetradecylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 2-0-eicosylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 2-0-decylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 3-octadecylthio-2-0-undecylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 2-0-dodecylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 3-octadecylthio-2-0-tetradecylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 2-0-eicosylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 3-octadecylthio-2-0-oleylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
- 2-0-linoleylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
- 3-hexadecylthio-2-0-oleylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,

- 3-hexadecylthio-2-0-linoleylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
2-0-oleylcarbamoyl-3-oleylthio-propan-1.2-diol-1-0-phosphocholine,
05 3-hexadecylthio-2-0-phenylcarbamoyl-1.2-diol-1-0-phosphocholine,
2-0-(2-fluorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(3-fluorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
10 2-0-(4-fluorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(2-chlorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
15 2-0-(3-chlorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(4-chlorophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(4-bromophenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
20 3-hexadecylthio-2-0-(2-methylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
3-hexadecylthio-2-0-(3-methylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
25 3-hexadecylthio-2-0-(4-methylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
3-hexadecylthio-2-0-(2-methoxyphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
3-hexadecylthio-2-0-(4-methylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
30 2-0-(2-ethoxyphenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(4-ethoxyphenyl)-carbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
35 3-hexadecylthio-2-0-(2-trifluoromethylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,

- 3-hexadecylthio-2-0-(3-trifluoromethylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
3-oleylthio-2-0-phenylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
05 3-linoleylthio-2-0-phenylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
3-octadecylthio-2-0-phenylcarbamoyl-propan-1.2-diol-1-0-phosphocholine,
2-0-(2-fluorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
10 2-0-(3-fluorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(4-fluorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
15 2-0-(2-chlorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(3-chlorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(4-chlorophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
20 2-0-(4-bromophenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(2-methylphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
25 2-0-(3-methylphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(4-methylphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(2-methoxyphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
30 2-0-(4-methoxyphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-(2-ethoxyphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
35 2-0-(4-ethoxyphenyl)-carbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,

- 3-Octadecylthio-2-0-(2-trifluoromethylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
3-Octadecylthio-2-0-(3-trifluoromethylphenyl)-carbamoyl-propan-1.2-diol-1-0-phosphocholine,
05 2-0-benzylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-benzylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,

Example 4

- 10 2-0-Dimethylcarbamoyl-3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine.

A mixture of 100 mg of 3-hexadecylthio-propan-1.2-diol-1-0-phosphocholine, 40 mg of dimethyl carbamic acid chloride and 60 mg of silver carbonate in 10 ml of chloroform is
15 stirred for 24 hours at 50°C, the solvent taken off in vacuo and the residue purified by column chromatography (silica gel//chloroform/methanol/water).

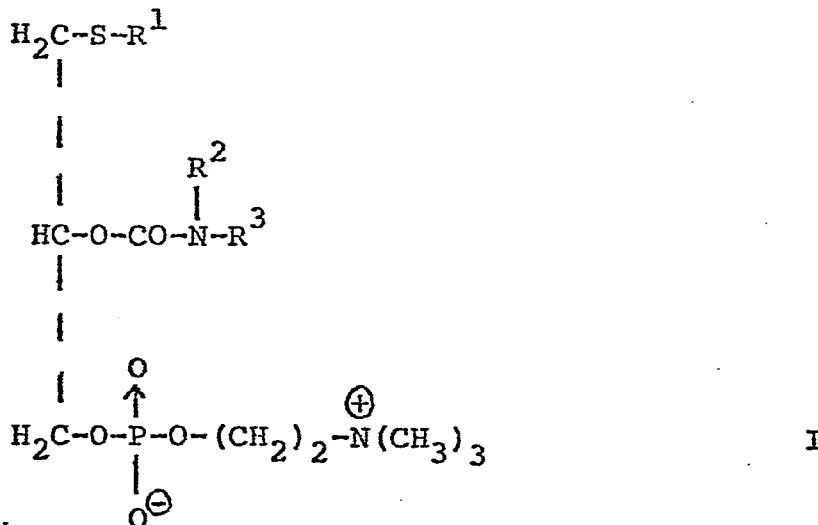
Yield: 83 mg. Mp: 239 to 241°C.

- 20 The following are prepared in a similar manner to example 4:

2-0-Dimethylcarbamoyl-3-octadecylthio-propan-1.2-diol-1-0-phosphocholine,
2-0-dimethylcarbamoyl-3-eicosylthio-propan-1.2-diol-1-0-phosphocholine.

PATENT CLAIMS:

1. 3-Alkylthio-2-0-carbamoyl-propan-1,2-diol-1-0-phosphocholines of the general formula I



5 wherein R¹ is a member selected from the group consisting
of the straight chain saturated and the straight chain
unsaturated hydrocarbon residues with 10 to 20 carbon
atoms, and R² and R³ which may be the same or different from
0 of the straight chain saturated, the straight chain un-
saturated, the branched chain saturated, and the branched
chain unsaturated hydrocarbon residues with 1 to 20 carbon
atoms, the unsubstituted phenyl group, the phenyl group
mono-substituted by C₁₋₃-alkyl, C₁₋₃-alkoxy, halogen or
5 trifluoromethyl, the benzyl group and hydrogen.

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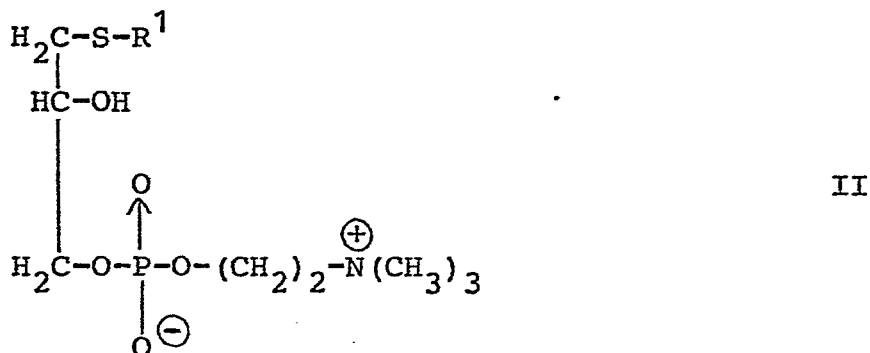
2. 3-Alkylthio-2-O-carbamoyl-propan-1.2-diol-1-O-phospho-
cholines as claimed in claim 1, wherein R^2 and R^3 which
may be the same or different from each other, are members
selected from the group consisting of the straight chain
05 saturated, the straight chain unsaturated, the branched
chain saturated, and the branched chain unsaturated hydro-
carbon residues with 1 to 10 carbon atoms, the unsubstituted
phenyl group, the phenyl group mono-substituted by methyl,
methoxy, ethoxy, fluoro, chloro, bromo or trifluoromethyl,
10 the benzyl group and hydrogen.

3. 3-Alkylthio-2-O-carbamoyl-propan-1.2-diol-1-O-phospho-
cholines according to claim 1 wherein R^1 is a member selec-
ted from the group consisting of the straight chain satu-
rated hydrocarbon residues with 16, 18 or 20 carbon atoms,
15 and R^2 and R^3 which may be the same or different from each
other, are members selected from the group consisting of
the methyl, ethyl and isopropyl residues and hydrogen.

4. 3-Alkylthio-2-O-carbamoyl-propan-1.2-diol-1-O-phospho-
cholines as claimed in claim 1, wherein R^1 is a member
20 selected from the group consisting of the straight chain
saturated and straight chain unsaturated hydrocarbon resi-
dues with 10 to 20 carbon atoms, R^2 is a hydrogen atom, and
 R^3 is a member selected from the group consisting of the
straight chain saturated and the straight chain unsaturated
25 hydrocarbon residues with 10 to 20 carbon atoms, R^1 and R^3
being the same or different.

5. 3-Alkylthio-2-O-carbamoyl-propan-1.2-diol-1-O-phospho-
cholines as claimed in claim 4, wherein R^1 is a member
selected from the group consisting of the straight chain
30 saturated hydrocarbon residues with 16 or 18 carbon atoms,
 R^2 is a hydrogen atom, and R^3 is a member selected from
the group consisting of the straight chain saturated hydro-
carbon residue with 16 or 18 carbon atoms, R^1 and R^3 being
the same or different.

6. Process for the preparation of compounds of the formula I according to claims 1 to 5 wherein a lyso-compound of the general formula II



05 wherein R¹ has the meaning given in formula I of claim 1, is reacted in an aprotic organic solvent with optional addition of a Lewis base as catalyst, with an isocyanate of the formula III



10 wherein R³ has the meaning given in formula I in claim 1.

7. Process for the preparation of compounds of the formula I according to claims 1 to 5 wherein a lyso-compound of the formula II is reacted in an inert organic solvent with optional addition of an acid acceptor, with the corresponding carbamic acid chlorides of the formula IV



wherein R² and R³ have the same meaning as given in formula I of claim 1.



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)
Y	EP-A-0 070 433 (FUJISAWA PHARMACEUTICAL CO.) * Page 1, lines 1-6; page 39, example 18; page 44, example 19; page 48, example 21; claims *	1	C 07 F 9/10 // A 61 K 31/685
Y	EP-A-0 043 472 (A. NATTERMANN & CIE.) * Page 2, lines 13-22; claims *	1	
Y	EP-A-0 072 936 (A. NATTERMANN & CIE.) * Page 3, lines 24-26; claims *	1	
			TECHNICAL FIELDS SEARCHED (Int. Cl. ³)
			C 07 F 9/00
The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 08-06-1984	Examiner BESLIER L.M.
<p>CATEGORY OF CITED DOCUMENTS</p> <p>X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document</p> <p>T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons</p> <p>& : member of the same patent family, corresponding document</p>			