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(54) **New o-acyl-alkanediol-phospholipids, processes for their preparation and pharmaceutical preparations containing them.**

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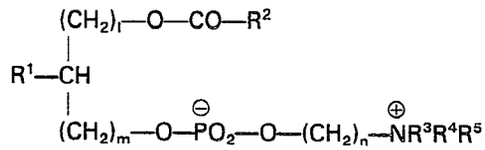
Description

The present invention relates to O-acyl-alkanediol-phospholipids and their use as active agents in preparations for the treatment of asthma in human beings.

The O-acyl-alkanediol-phospholipids of the invention correspond to the general formula I



I

wherein R^1 is a straight or branched chain alkyl residue having from 10 to 20 carbon atoms, a straight or branched chain alkenyl group having one double bond and having from 10 to 20 carbon atoms, R^2 is hydrogen, a straight or branched chain alkyl residue having from 1 to 4 carbon atoms, a straight or branched chain alkoxy residue having from 1 to 4 carbon atoms or the group $—NR^6R^7$, R^3, R^4 and R^5 which may be the same or different from each other, each are hydrogen or an alkyl residue having from 1 to 4 carbon atoms, R^6 and R^7 which may be the same or different from each other, each represent hydrogen, an alkyl residue having from 1 to 20 carbon atoms or an alkenyl group having one double bond and from 1 to 20 carbon atoms, the phenyl group or a phenyl group substituted by C_{1-3}-alkyl, C_{1-3}-alkoxy, halogen or trifluoromethyl, or the benzyl group, l and m which may be the same or different from each other, represent 0 or 1 except that l and m may not both be zero, and n represents a whole number from 2 to 4.

R^3, R^4 and R^5 preferably are methyl. The index n is preferably 2.

From Japanese Patent Publication No. 58—13592 of January 26, 1983 (Patent Abstracts of Japan, Vol. 7, No. 83 (C—160), 1228 of April 7, 1983) there are known similar phosphocholine derivatives which differ from the compounds not only structurally but in that the compounds of the prior art are used as antihypertensive agent while the compounds of the present invention are characterized by a pronounced bronchospasmolytic activity which makes them most useful in the treatment of asthma.

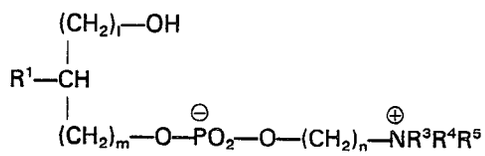
Examples of compounds of the invention are:

1-O-acetyl-1.2-eicosandiol-2-O-phosphocholine
2-O-acetyl-1.2-octadecandiol-1-O-phosphocholine
1-O-acetyl-1.2-octadecandiol-2-O-phosphocholine
2-O-acetyl-1.2-dodecandiol-1-O-phosphocholine
2-O-acetyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-acetyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-acetyl-1.2-eicosandiol-1-O-phosphocholine
2-O-acetyl-1.2-docosandiol-1-O-phosphocholine
1-O-ascetyl-1.2-dodecandiol-2-O-phosphocholine
1-O-acetyl-1.2-tetradecandiol-2-O-phsophochooline
1-O-acetyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-acetyl-1.2-docosandiol-2-O-phosphocholine
2-O-formyl-1.2-eicosandiol-1-O-phosphocholine
2-O-propionyl-1.2-eicosandiol-1-O-phosphocholine
2-O-butyryl-1.2-eicosandiol-1-O-phosphocholine
(2-acetoxy-octadecyl)-triethylammonioethyl phosphate
(2-acetoxy-octadecyl)-tripropylammonioethyl phosphate
(2-acetoxy-octadecyl)-tributylammonioethyl phosphate
(2-acetoxy-octadecyl)-dimethylammonioethyl phosphate
3-O-acetyl-2-octdadecyl-1.3-propandiol-1-O-phosphocholine
3-O-2-decyl-1.3-propandiol-1-O-phosphocholine
3-O-acetyl-2-dodecyl-1.3-propandiol-1-O-phosphocholine
3-O-aceytl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
3-O-acetyl-2-hexadecyl-1.3-propandiol-1-O-phosphocholine
3-O-acetyl-2-eicosyl-1.3-propandiol-1-O-phosphocholine
(2-acetoxymethyl-eicosyl)-trimethylammoniopropyl phosphate
(2-acetoxymethyl-eicosyl)-trimethylammoniobutyl phosphate
(2-acetoxymethyl-eicosyl)-dimethylammonioethyl phosphate
1-O-methylcarbamoyl-1.2-octadecandiol-2-O-phosphocholine
1-O-ethylcarbamoyl-1.2-octadecandiol-2-O-phosphocholine
1-O-benzylcarbamoyl-1.2-octadecandiol-2-O-phosphocholine
1-O-carbamoyl-1.2-octadecandiol-2-O-phosphocholine
2-O-methylcarbamoyl-1.2-octadecandiol-1-O-phosphocholine
2-O-ethylcarbamoyl-1.2-octadecandiol-1-O-phosphocholine
1-O-ethylcarbamoyl-1.2-eicosandiol-2-O-phosphocholine
1-O-methylcarbamoyl-1.2-eicosandiol-2-O-phosphocholine

1-O-benzylcarbamoyl-1.2-eicosandiol-2-O-phosphocholine
1-O-carbamoyl-1.2-eicosandiol-2-O-phosphocholine
3-O-methylcarbamoyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine
3-O-ethylcarbamoyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine
2-O-methylcarbamoyl-1.2-dodecandiol-1-O-phosphocholine
2-O-ethylcarbamoyl-1.2-dodecandiol-1-O-phosphocholine
2-O-methylcarbamoyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-ethylcarbamoyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-methylcarbamoyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-ethylcarbamoyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-methylcarbamoyl-1.2-eicosandiol-1-O-phosphocholine
2-O-ethylcarbamoyl-1.2-eicosandiol-1-O-phosphocholine
2-O-methylcarbamoyl-1.2-docosandiol-1-O-phosphocholine
2-O-ethylcarbamoyl-1.2-docosandiol-1-O-phosphocholine
1-O-methylcarbamoyl-1.2-dodecandiol-2-O-phosphocholine
1-O-ethylcarbamoyl-1.2-dodecandiol-2-O-phosphocholine
1-O-methylcarbamoyl-1.2-tetradecandiol-2-O-phosphocholine
1-O-ethylcarbamoyl-1.2-tetradecandiol-2-O-phosphocholine
1-O-methylcarbamoyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-ethylcarbamoyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-methylcarbamoyl-1.2-docosandiol-2-O-phosphocholine
1-O-ethylcarbamoyl-1.2-docosandiol-2-O-phosphocholine
2-O-phenylcarbamoyl-1.2-eicosandiol-1-O-phosphocholine
2-O-[(4-chlorophenyl)-carbamoyl]-1.2-eicosandiol-1-O-phosphocholine
2-O-hexadecylcarbamoyl-1.2-eicosandiol-1-O-phosphocholine
2-O-oleylcarbamoyl-1.2-eicosandiol-1-O-phosphocholine
2-decyl-3-O-methylcarbamoyl-1.3-propandiol-1-O-phosphocholine
2-dodecyl-3-O-methylcarbamoyl-1.3-propandiol-1-O-phosphocholine
3-O-methylcarbamoyl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
2-hexadecyl-3.O-methylcarbamoyl-1.3-propandiol-1-O-phosphocholine
2-eicosyl-3.O-methylcarbamoyl-1.3-propandiol-1-O-phosphocholine
2-decyl-3.O-ethylcarbamoyl-1.3-propandiol-1-O-phosphocholine
2-dodecyl-3-O-ethylcarbamoyl-1.3-propandiol-1-O-phosphocholine
3-O-ethylcarbamoyl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
3-O-ethylcarbamoyl-2-hexadecyl-1.3-propandiol-1-O-phosphocholine
2-eicosyl-3-O-ethylcarbamoyl-1.3-propandiol-1-O-phosphocholine
2-O-dimethylcarbamoyl-1.2-octadecandiol-1-O-phosphocholine
2-O-dimethylcarbamoyl-1.2-dodecandiol-1-O-phosphocholine
2-O-dimethylcarbamoyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-dimethylcarbamoyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-dimethylcarbamoyl-1.2-eicosandiol-1-O-phosphocholine
2-O-dimethylcarbamoyl-1.2-docosandiol-1-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-dodecandiol-2-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-tetradecandiol-2-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-octadecandiol-2-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-eicosandiol-2-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-docosandiol-2-O-phosphocholine
2-decyl-3-O-dimethylcarbamoyl-1.3-propandiol-1-O-phosphocholine
3-O-dimethylcarbamoyl-2-dodecyl-1.3-propandiol-1-O-phosphocholine
3-O-dimethylcarbamoyl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
3-O-dimethylcarbamoyl-2-hexadecyl-1.3-propandiol-1-O-phosphocholine
3-O-dimethylcarbamoyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine
3-O-dimethylcarbamoyl-2-eicosyl-1.3-propandiol-1-O-phosphocholine
2-O-methoxycarbonyl-1.2-dodecandiol-1-O-phosphocholine
2-O-ethoxycarbonyl-1.2-dodecandiol-1-O-phosphocholine
2-O-methoxycarbonyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-ethoxycarbonyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-methoxycarbonyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-ethoxycarbonyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-methoxycarbonyl-1.2-octadecandiol-1-O-phosphocholine
2-O-ethoxycarbonyl-1.2-octadecandiol-1-O-phosphocholine
2-O-methoxycarbonyl-1.2-eicosandiol-1-O-phosphocholine
2-O-ethoxycarbonyl-1.2-eicosandiol-1-O-phosphocholine
2-O-methoxycarbonyl-1.2-docosandiol-1-O-phosphocholine

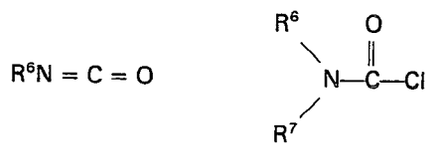
2-O-ethoxycarbonyl-1.2-docosandiol-1-O-phosphocholine
1-O-methoxycarbonyl-1.2-dodecandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-dodecandiol-2-O-phosphocholine
1-O-methoxycarbonyl-1.2-tetradecandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-tetradecandiol-2-O-phosphocholine
1-O-methoxycarbonyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-methoxycarbonyl-1.2-octadecandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-octadecandiol-2-O-phosphocholine
1-O-methoxycarbonyl-1.2-eicosandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-eicosandiol-2-O-phosphocholine
1-O-methoxycarbonyl-1.2-docosandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-docosandiol-2-O-phosphocholine
2-decyl-3-O-methoxycarbonyl-1.3-propandiol-1-O-phosphocholine
2-decyl-3-O-ethoxycarbonyl-1.3-propandiol-1-O-phosphocholine
2-dodecyl-3-O-methoxycarbonyl-1.3-propandiol-1-O-phosphocholine
2-dodecyl-3-O-ethoxycarbonyl-1.3-propandiol-1-O-phosphocholine
3-O-methoxycarbonyl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
3-O-ethoxycarbonyl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
2-hexadecyl-3-O-methoxycarbonyl-1.3-propandiol-1-O-phosphocholine
3-O-ethoxycarbonyl-2-hexadecyl-1.3-propandiol-1-O-phosphocholine
3-O-methoxycarbonyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine
3-O-ethoxycarbonyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine
2-eicosyl-3-O-methoxycarbonyl-1.3-propandiol-1-O-phosphocholine
2-eicosyl-3-O-ethoxycarbonyl-1.3-propandiol-1-O-phosphocholine

O-Carbamoyl-alkandiol-phospholipids of the present invention are prepared by reacting lyso-phospholipids of the formula II



II

in which R^1, R^3, R^4, R^5, l, m, n have the meanings given for formula I, with carbonic acid derivatives of the formula III or IV



III IV

in which R^6 and R^7 have the meanings given for formula I, in an inert organic solvent, e.g. chloroform, dimethyl formamide, N-methyl acetamide, with optional addition of a catalyst or a base such as dimethylaminopyridine, pyridine, triethylamine, silver carbonate, barium carbonate, especially when using compounds of the formula IV.

Compounds of the formula I with $R^6 = R^7 = H$ can be prepared advantageously by hydrogenating, with hydrogen, compounds of the formula I with R^6 = benzyl and R^7 = H in a suitable organic solvent, e.g. methanol, ethanol, ether, dioxan or mixtures thereof with each other and with water, with splitting-off of the benzyl group in the presence of a conventional hydrogenation catalyst, e.g. palladium/active carbon.

Examples of useful starting compounds of the formula II are:

1.2-Dodecandiol-1-O-phosphocholine
1.2-tridecandiol-1-O-phosphocholine
1.2-tetradecandiol-1-O-phosphocholine
1.2-pentadecandiol-1-O-phosphocholine
1.2-hexadecandiol-1-O-phosphocholine
1.2-heptadecandiol-1-O-phosphocholine
1.2-octadecandiol-1-O-phosphocholine
1.2-nonadecandiol-1-O-phosphocholine
1.2-eicosandiol-1-O-phosphocholine
1.2-heneicosandiol-1-O-phosphocholine
1.2-docosandiol-1-O-phosphocholine
1.2-dodecandiol-2-O-phosphocholine

1.2-tridecandiol-2-O-phosphocholine
1.2-tetradecandiol-2-O-phosphocholine
1.2-pentadecandiol-2-O-phosphocholine
1.2-hexadecandiol-2-O-phosphocholine
1.2-heptadecandiol-2-O-phosphocholine
1.2-octadecandiol-2-O-phosphocholine
1.2-nonadecandiol-2-O-phosphocholine
1.2-eicosandiol-2-O-phosphocholine
1.2-heneicosandiol-2-O-phosphocholine
1.2-docosandiol-2-O-phosphocholine
2-decyl-1.3-propandiol-1-O-phosphocholine
2-undecyl-1.3-propandiol-1-O-phosphocholine
2-dodecyl-1.3-propandiol-1-O-phosphocholine
2-tridecyl-1.3-propandiol-1-O-phosphocholine
2-tetradecyl-1.3-propandiol-1-O-phosphocholine
2-pentadecyl-1.3-propandiol-1-O-phosphocholine
2-hexadecyl-1.3-propandiol-1-O-phosphocholine
2-heptadecyl-1.3-propandiol-1-O-phosphocholine
2-octadecyl-1.3-propandiol-1-O-phosphocholine
2-nonadecyl-1.3-propandiol-1-O-phosphocholine
2-eicosyl-1.3-propandiol-1-O-phosphocholine
2-oleyl-1.3-Propandiol-1-O-phosphocholine
2-(15-methyl-hexadecyl)-1.3-propandiol-1-O-phosphocholine
2-(17-methyl-hexadecyl)-1.3-propandiol-1-O-phosphocholine,

the lyso-compounds being usable in either their R- or their S- form or as a racemic mixture,

Examples of starting compounds of the formula III are: Methyl isocyanate, ethyl isocyanate, propyl isocyanate, isopropyl isocyanate, butyl isocyanate, allyl isocyanate, hexyl isocyanate, octyl isocyanate, decyl isocyanate, undecyl isocyanate, dodecyl isocyanate, tetradecyl isocyanate, hexadecyl isocyanate, octadecyl isocyanate, eicosyl isocyanate, oleyl isocyanate, phenyl isocyanate, 4-chlorophenyl isocyanate, 3-fluorophenyl isocyanate, 4-fluorophenyl isocyanate, p-tolyl isocyanate, p-methoxyphenyl isocyanate, p-trifluoromethyl isocyanate, m-trifluoromethyl isocyanate, benzyl isocyanate.

Preferred examples of the starting compounds of the formula IV are carbamic acid chlorides whose substituents R^6, R^7 contain a short-chain hydrocarbon residue with 1—4 carbon atoms, e.g. dimethylcarbamic acid chloride, diethylcarbamic acid chloride, dipropylcarbamic acid chloride, dibutylcarbamic acid chloride, methylethylcarbamic acid chloride, methylpropylcarbamic acid chloride, methylbutylcarbamic acid chloride, ethylpropylcarbamic acid chloride, butylpropylcarbamic acid chloride, butylethylcarbamic acid chloride.

O-Alkanol- and O-alkoxycarbonyl-alkanediol-phospholipids according to the present invention are likewise prepared from the lyso-compond of the formula II, by reacting the latter with the corresponding alkanoic acid halides, alkanoic acid anhydrides or chloroformic acid esters of the formula V

$$X—CO—R^2 \qquad V$$

in which X is any halogen, preferably chlorine, or the residue R^2—CO— (anhydrides) and R^2 signifies a straight or branched chain alkyl or alkoxy residue according to formula I, in an inert organic solvent, e.g. chloroform, dimethylformamide, with optional addition of an acid acceptor, e.g. pyridine, triethylamine.

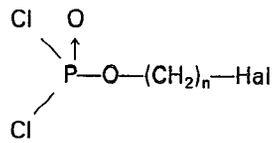
Examples of starting compounds of the formula V are: Acetyl chloride, propionyl chloride, butyryl chloride, isobutyryl chloride, acetic anhydride, propionic anhydride, butyric anhydride, isobutric anhydride, methyl chloroformate, ethyl chloroformate, propyl chloroformate, isopropyl chloroformate, butyl chloroformate, isobutyl chloroformate.

In the case where R^2 = H, mixed anhydrides, e.g. formic/acetic anhydride can also be used.

O-Acyl-alkandiol-phospholipids of the general formula I are also available form alcohols of the formula VI

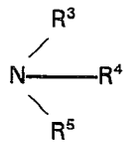
$$\begin{array}{c} (CH_2)_l—O—CO—R^2 \\ | \\ R^1—CH \\ | \\ (CH_2)_m—OH \end{array} \qquad VI$$

in which R^1, R^2, l, m have the meanings given for formula I, by reacting them with dichlorophosphoric acid ω-halo-alkanoic acid esters of the formula VII



VII

in which n has the meaning given for formula I and Hal is a chlorine or bromine atom, in an inert organic solvent, with optional use of an auxiliary base e.g. pyridine or triethylamine, and subsequently treating with an amine of the formula VIII



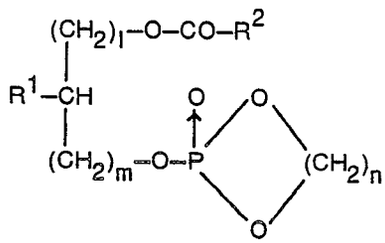
VIII

in which R^3, R^4 and R^5 have the meanings given for formula I, in an inert organic solvent e.g. toluene, dioxan, tetrahydrofuran, optionally under pressure. Cf in this connection H. K. Mangold, Angew. Chem. *92,* 550—560 (1979; H. Eibl, Chem. and Phys. of Lipids *26,* 405—429 (1980).

he compounds of formula I can also be prepared by phosphorylating compounds of the formula VI with phosphorus oxytrichloride, and afterwards reacting with an alkandiol of the formula IX

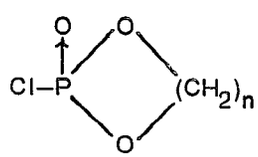
$$HO—(CH_2)_n—OH \qquad IX$$

in which n has the meaning given for formula I, with optional use of auxiliary bases e.g. triethylamine, and with use of inert solvents e.g. tetrahydrofuran, to yield cyclic intermediates of the formula X



X

in which R^1, R^2, l, m, n have the meanings given for formula I. CF H. Eibl, Phospholipid Synthesis in Knight (Publisher) Liposomes, Elsevier 1981, pp 19—50. The intermediates of the formula X can also be prepared by reacting compounds of the formula VI with a cyclic phosphorus compound of the formula XI



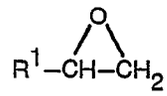
XI

in which n has the meaning given for formula I, in an inert organic solvent with addition of an auxiliary base. Cf N. S. Chandrakumur et al., Tetrahedron Lett. *23,* 1043 (1982); Biochim. Biophys. Acta *711,* 357 (1982). The intermediates C can be converted in a simple manner into the compounds of the formula I, e.g. by treatment with an amine of the formula VIII, in an organic solvent, optionally under pressure. Cf N. T. Thuong and P. Chabrier, Bull. Soc. Chim. Fr. *1974,* 667 ff.

Examples of starting compounds of the formula VII are: Dichlorophosphoric acid 2-bromoethyl ester, dichlorophosphoric acid 2-dchloroethyl ester, dichlorophosphoric acid 3-bromopropyl ester, dichlorophosphoric acid 4-bromo-butyl ester.

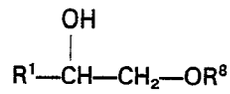
Preferred starting compounds of the formula VIII are secondary and tertiary amines, e.g. dimethylamine, diethylamine, dipropylamine, dibutylamine, trimethylamine, triethylamine, tripropylamine, tributylamine, ethylmethylamine, methylpropylamine, ethylpropylamine, butylmethylamine, butylethylamine, butylpropylamine, dimethylethylamine, dimethylpropylamine, butyldimethylamine, diethylmethylamine, diethylpropylamine, butyldiethylamine, dipropylmethylamine, dipropylethylamine, butyldipropylamine, dibutylmethylamine, dibutylethylamine, dibutylpropylamine, ethylmethylpropylamine, butylmethylpropylamine, butylethylmethylamine, butylethylpropylamine.

The lyso-compounds with l = 1 and m = 0, used as starting compounds of the formula II are prepared by reacting epoxides of the formula XII



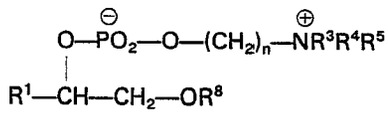
XII

in which R^1 has the meaning given for formula I, in the form of the pure substance or dissolved in an inert organic solvent, with benzyl alcohol or a comparable protecting group reagent in the presence of a base, preferably at temperatures of 0—150°C, to yield a 1—O-protected diol of the formula XIII



XIII

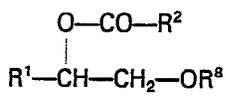
Apart from benzyl or a comparable protecting group, the residue R^8, in a special case, can also be trityl or substituted trityl, of XIII is prepared by the conventional procedure from the original diol and trityl halides or substituted trityl halides. For their part the compounds XIII are transformed into the phospholipids of the formula XIV



XIV

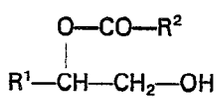
analogously to the previously described phosphorylation procedure. The compounds XIV are hydrogenated with hydrogen in a suitable organic solvent, e.g. methanol, ethanol, ether, dioxan or mixtures thereof with each other and with water, with splitting-off of the benzyl or trityl group in the presence of one of the conventional hydrogenation catalysts, e.g. palladium/active carbon, yielding the desired lyso-compounds II with l = 1 and m = 0. In the case where R^8 = trityl or substituted trityl, the conventional ether scissions can be carried out with the aid of organic or inorganic acids in aqueous/organic media.

The lyso-compounds with l = 0 and m = 1, used as starting compounds of the formula II, are prepared from the compounds XIII, by converting the latter into the acyl derivatives XV



XV

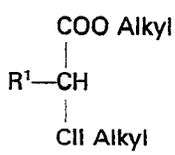
in which R^2 has the meaning given for formula I and R^8 that given in formula XIII, by means of a reactive acid derivative, e.g. an acid halide or anhydride, optionally in the presence of an acid acceptor such as triethylamine, pyridine, inorganic oxides, carbonates, etc. The acyl derivatives XV are hydrogenated with hydrogen in a suitable organic solvent, e.g. methanol, ethanol, ether, dioxan or mixtures thereof with each other and with water, with splitting-off of the benzyl or trityl group in the presence of one of the conventional hydrogenation catalyst, e.g. palladium/active carbon, yielding compounds of the formula XVI



XVI

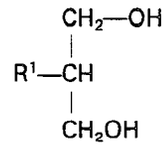
The compounds of the formula XVI are converted into the phospholipids of the formula I with R^2 = hydrogen, alkyl, alkoxy analogously to the previously described processes for the phosphorylation of VI, and the phospholipids, if desired, are converted by mild alkaline hydrolysis to the lyso-compounds of the formula II with l = 0 and m = 1.

The lyso-compounds with l = 1 and m = 1, used as starting compounds of the formula II, are prepared by reducing substituted malonic acid diesters of the formula XVII



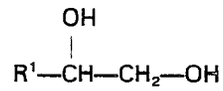
XVII

in which R^1 has the meaning given in formula I and Alkyl represents a suitable alkyl residue, preferably methyl or ethyl, with an appropriate reducing agent e.g. lithium aluminium hydride, to yield the diols of the formula XVIII



XVIII

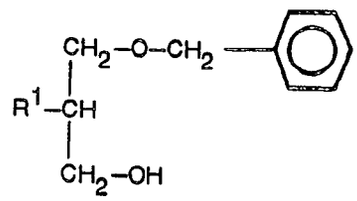
The diols XVIII can, just like the diols of the formula XIX



XIX

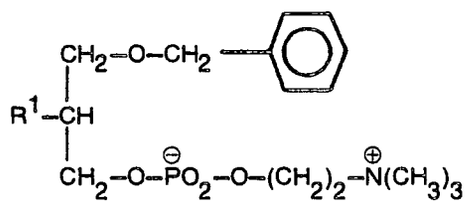
in which R^1 likewise has the meaning given for formula I, be converted directly into the lyso-compounds II with l = m = 1 or l = 0, m = 1, analogously to the previously described process for the phosphorylation of VI.

On the other hand the compounds XVIII can also be converted with benzyl halides or similar protecting group reagents by the conventional methods to the monobenzyl ethers XX



XX

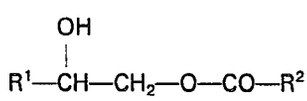
from which — analogously to the processes previously described for the phosphorylation of VI — the phospholipids XXI can be obtained



XXI

The phospholipids XXI yield the lyso-compounds of the formula II with l = m = 1, analogously to the hydrogenation or scission of a similar protecting group described for the preparation of XVI from XV.

Phospholipids of the formule I with R^2 = hydrogen or alkyl and l = 1 as well as m = 0 can also be prepared by opening epoxides of the formula XII with the corresponding acids R^2COOH to yield the ester-alcohols XXII



XXII

according to the procedure given by U. Zeidler in Fette, Seifen, Anstrichmittel *83* (2), 57 (1981), and treating said ester-alcohols similarly to the process described for the phosphorylation of VI.

The present invention relates likewise to the use of the compounds of formula I as active agents in pharmaceutical preparations for the treatment of asthma in humans wherein such a preparation is administered to a human being suffering from asthma in the dosages given below. 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. 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 often, preferably 2 to 3 times daily.

The preparation of the compounds of the invention is described in more detail by the following examples. The melting points given were measured with a Beuchi 510 melting point determination apparatus and are uncorrected.

Example 1
1-O-Acetyl-1.2-eicosandiol-2-O-phosphocholine.

a) 1-O-Acetyl-1.2-eicosandiol.
95 g. of 1.2-Epoxyeicosane is mixed with 21 g of acetic acid and about 0.1 g of sodium acetate and the mixture stirred for 6 hours at 130°C. The mixture is evaporated and the residue purified by column chromatography (silica gel/chloroform).
Yield: 74 g; Mp: 73°C.

b) (1-Acetoxymethyl-nonadecyl)-2-bromoethyl phosphate.
13 g of 1-O-acetyl-1.2-eicosandiol is dissolved in 200 ml of pyridine and 17.7 g of 2-bromoethylphosphoric acid dichloride are added dropwise with ice cooling. After about 2 hours of stirring at room temperature, 200 ml of water are added and the mixture further stirred for half an hour at room temperature. After dilution with water, it is extracted with chloroform, the chloroform phase is washed with water and dried over sodium sulphate. After evaporation of the solvent in vacuo the residue is purified by column chromatography (silica gel//chloroform/methanol).
Yield:(10.4 g (oil).

c) 1-O-Acetyl-1.2-eicosandiol-2-O-phosphocholine.
9 g of (1-Acetoxymethyl-nonadecyl)-2-bromoethyl phosphate is dissolved in 100 ml of toluene, 15 ml of 20% trimethylamine solution in toluene is added and the mixture stirred for 5 hours at 60°C in the autoclave. After evaporation of the solvent in vacuo the residue is purified by column chromatography (silica//chloroform/methanol).
Yield: 4.2 g; Mp 194—197°C.

Example 2
2-O-Acetyl-1.2-octadecandiol-1-O-phosphocholine.

a) 1-O-Benzyl-1.2-octadecandiol.
216 g of benzyl alcohol is added dropwise to a suspension of 9.8 g of sodium hydride in toluene at boiling point. When the evolution of hydrogen has ceased the mixture is cooled and, one after the other, 268 g of 1.2-epoxyoctadecane and 2.73 g of 18-Krone-6 are added. The mixture is stirred at 60°C to the end of the reaction, cooled, washed with water and dried over magnesium sulphate. After removal of the excess benzyl alcohol and solvent the residue is purified by column chromatography (silica gel/chloroform).
Yield: 302 g; Mp: 48°C.

b) 2-O-Acetyl-1-O-benzyl-1.2-octadecandiol.
89 g of 1-O-benzyl-1.2-octadecandiol is reacted with 48 g of acetic anhydride and the mixture heated under reflux for 1 hour. After removal of the excess acetic anhdride and acetic acid in vacuo the residue is further worked up directly.
Yield: 97 g (oil).

c) 2-O-Acetyl-1.2-octadecandiol.
15 g of the 2-O-acetyl-1-O-benzyl-1.2-octadecandiol is dissolved in 50 ml of ethanol, the solution is then hydrogenated with hydrogen at 0°C for 4 hours after addition of 1.5 g of palladium/active carbon. The active carbon is filtered off and the filtrate cooled to −20°C. The precipitated solid is filtered off and dried in a high vacuum.
Yield: 9.1 g; Mp: 46 to 49°C.

d) (2-Acetoxy-octadecyl)-2-bromoethyl phosphate.
6 g of 2-O-acetyl-1.2-octadecandiol is dissolved in 100 ml of chloroform and, one after the other, 8 ml of pyridine and 6.6 g of 2-bromoethylphosphoric acid dichloride are added at 0°C. After stirring for 1 hour with ice cooling and addition of a little ice water, the mixture is again stirred for half an hour at 0°C. The organic phase is separated, washed with water and dried over sodium sulphate. After evaporation of the solvent in vacuo the residue is purified by column chromatography (silica gel//chloroform/methanol).
Yield: 5.2 g (oil).

e) 2-O-Acetyl-1.2-octadecandiol-1-O-phosphocholine.
3 g of (2-acetoxy-octadecyl)-2-bromoethyl phosphate is dissolved in 100 ml of toluene, 10 ml of 20% trimethylamine solution in toluene is added to the solution, and the mixture is stirred for 5 hours at 60°C in the autoclave. After evaporation of the solvent in vacuo the residue is purified by column chromatography (silica gel//chloroform/methanol).
Yield: 2.1 g; Mp: 228°C.

Example 3
1-O-Acetyl-1.2-octadecandiol-2-O-phosphocholine.

a) (1-Acetoxymethyl-heptadecyl)-2-bromoethyl phosphate.

70 g of 1-O-acetyl-1.2-octadecandiol (prepared similarly to 1-O-acetyl-1.2-eicosandiol) are dissolved in 400 ml of pyridine and 77 g of 2-bromoethyl phosphoric acid dichloride are added dropwise with ice cooling. After about 2 hours of stirring at room temperature 400 ml of water are added and the mixture further stirred for half an hour at room temperature. After dilution with water the mixture is extracted with chloroform, the chloroform phase washed with 5% hydrochloric acid and water, dried over sodium sulphate and the solvent removed. The crude product (110 g) is worked up further without purification.

b) 1-O-Acetyl-1.2-octadecandiol-2-O-phosphocholine.

110 g of (1-Acetoxymethyl-heptadecyl)-2-bromoethyl) phosphate (crude product) are dissolved in 500 ml of toluene, 300 ml of 20% trimethylamine solution in toluene are added and the mixture stirred for 8 hours at 60°C in the autoclave. After evaporation of the solvent in vacuo the residue is purified by column chromatography (silica gel//chloroform/methanol).

Yield: 50.5 g; Mp: 217 to 224°C.

Example 4
1-O-Acetyl-1.2-octadecandiol-2-O-phosphocholine (from 1.2-octadecandiol-2-O-phosphocholine).

1 g of 1.2-octadecandiol-2-O-phosphocholine is dissolved in 20 ml of chloroform and 0.7 g of acetic anhydride are added. The mixture is stirred until the reaction is complete, evaporated to dryness in vacuo and the residue is freeze-dried after dissolving in water.

Yield: 1.1 g; Mp: 218 to 225°C.

The following are prepared analogously to examples 1—4:

2-O-acetyl-1.2-dodecandiol-1-O-phosphocholine
2-O-acetyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-acetyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-acetyl-1.2-eicosandiol-1-O-phosphocholine
2-O-acetyl-1.2-docosandiol-1-O-phosphocholine
1-O-acetyl-1.2-dodecandiol-2-O-phosphocholine
1-O-acetyl-1.2-tetradecandiol-2-O-phosphocholine
1-O-acetyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-acetyl-1.2-docosandiol-2-O-phosphocholine
2-O-formyl-1.2-eicosandiol-1-O-phosphocholine
2-O-propionyl-1.2-eicosandiol-1-O-phosphocholine
2-O-butyryl-1.2-eicosandiol-1-O-phosphocholine
(2-acetoxy-octadecyl)-triethylammonioethyl phosphate
(2-acetoxy-octadecyl)-tripropylammonioethyl phosphate
(2-acetoxy-octadecyl)-tributylammonioethyl phosphate
(2-acetoxy-octadecyl)-dimethylammonioethyl phosphate

Example 5
3-O-Acetyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine.

a) 2-Octadecylmalonic acid diethyl ester.

One after the other, 160 g of diethyl malonate and 350 g of bromo octadecane are added dropwise to a hot solution of 23 g of sodium hydroxide in 500 ml of absolute ethanol, and the mixture heated under reflux for about 12 hours, until the solution gives a nearly neutral reaction. Then the solvent is removed, the residue shaken with water and ether, the ether phase dried over sodium sulphate and the ether evaporated. The residual oil is distilled in vacuo.

Yield: 311 g ($Bp_{0.3mbar}$ 195 to 200°C); Mp: 39 to 41°C.

b) 2-Octadecyl-1.3-propandiol.

150 g of diethyl 2-octadecylmalonate are dissolved in 200 ml of absolute tetrahydrofuran and the solution slowly added dropwise to 14 g of lithium aluminium hydride in 300 ml of tetrahydrofuran. The mixture is boiled for 4 hours under reflux, reacted with isopropanol with ice cooling and thereafter with 10% sulfuric acid, until the precipitate of aluminium hydroxide just redissolves. The greater part of the solvent is removed in vacuo and the residue treated with chloroform. 2-Octadecyl-1.3-propandiol precipitates from the chloroform phase and is filtered off and dried.

Yield: 248 g; Mp: 88°C.

c) 2-Benzyloxymethyl-eicosanol.

110 g 2-octadecyl-1.3-propandiol are added at 80°C to a suspension of 16 g of sodium hydride in 1.5 l of dimethylformamide. When hydrogen evolution has finished, 42 g of benzyl chloride dissolved in 500 ml of dimethylformamide are added dropwise with strong agitation. The mixture is stirred for 8 hours at 80°C, the solvent substantially removed in vacuo and water added. Thereupon the mixture is extracted with chloroform, the chloroform phase washed with water and dried over sodium sulphate. After removal of the solvent the residue is stirred with hexane, unreacted starting substance is filtered off and the filtrate is evaporated. The residue from the filtrate is purified by column chromatogrpahy (silica gel//hexane/ethyl acetate).

Yield: 76 g.

d) (2-Benzyloxymethyl-eicosyl)-2-bromoethyl phosphate.

20 g of 2-benzyloxymethyl-eicosanol, dissolved in a little of chloroform, is added dropwise to an ice-cooled mixture of 17 g of 2-bromoethylphosphoric acid dichloride, 8 ml of pyridine and 200 ml of chloroform. The mixture is stirred for 5 hours, treated with 200 ml of water and stirred again for half an hour. The organic phase is separated, washed with water and dried over sodium sulphate. The solvent is removed and the residue is purified by column chromatography (silica gel//chloroform/methanol).

Yield: 17.5 g (oil).

e) 3-O-Benzoyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine.

17.5 g of (2-benzyloxymethyl-eisocyl)-2-bromoethyl phosphate is dissolved in 150 ml of toluene, 20 ml of 33% alcoholic trimethylamine solution is added and the mixture stirred for 5 hours at 70°C. After evaporation of the solvent in vacuo the residue is purified by column chromatography (silica gel// chloroform/methanol).

Yield: 12 g; Mp: 237 to 242°C.

f) 2-Octadecyl-1.3-propandiol-1-O-phosphocholine.

15 g of 3-O-benzyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine are dissolved in 300 ml of ethanol, the solution is hydrogenated with hydrogen after addition of 1.5 g of palladium/active carbon with gradual addition of about 100 ml of water. After the active carbon has been filtered off, the residue is evaporated and worked up further without purification.

Yield: 10.1 g) Mp: 240°C.

g) 3-O-Acetyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine.

1 g of 2-octadecyl-1.3-propandiol-1-O-phosphocholine is dissolved in 20 ml of chloroform and 5 ml of acetic anhydride is added. The mixture if stirred at 80°C until reaction is complete, evaporated to dryness in vacuo and the residue is washed with acetone.

Yield: 10 g; Mp: 207 to 220°C.

The following were prepared analogously to example 5:

3-O-acetyl-2-decyl-1.3-propandiol-1-O-phosphocholine
3-O-acetyl-2-dodecyl-1.3-propandiol-1-O-phosphocholine
3-O-acetyl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
3-O-acetyl-2-hexadecyl-1.3-propandiol-1-O-phosphocholine
3-O-acetyl-2-eicosyl-1.3-propandiol-1-O-phosphocholine
(2-acetoxymethyl-eicosyl)-trimethylammoniopropyl phosphate
(2-acetoxymethyl-eicosyl)-trimethylammoniobutyl phosphate
(2-acetoxymethyl-eicosyl)-(dimethylammonioethyl)phosphate

Example 6
1-O-Methylcarbamoyl-1.2-octadecandiol-2-O-phosphocholine.

a) 1.2-Octadecandiol-2-O-phosphocholine.

10 g of 1-O-acetyl-1.2-octadecandiol-2-O-phosphocholine are dissolved in 100 ml of absolute ethanol and 2.8 g of potassium carbonate added. The mixture is stirred at room temperature for 24 hours, filtered and evaporated to dryness in vacuo. The residue is shaken up with acetone, the solid substance filtered off and dried.

Yield: 7.5 g; Mp: 273°C.

b) 1-O-Methylcarbamoyl-1.2-octadecandiol-2-O-phosphocholine.

2 g of 1.2-octadecandiol-2-O-phosphocholine are dissolved in 20 ml of chloroform and 1 ml of dimethylformamide, and 0.5 g of methyl isocyanate are added dropwise. The mixture is stirred at room temperature for 24 hours, the solvent removed and the residue purified by column chromatography (silica gel/chloroform/methanol).

Yield: 1.2 g; Mp: about 240°C (dec.).

Example 7
1-O-Ethylcarbamoyl-1.2-octadecandiol-2-O-phosphocholine.

2 g of 1.2-octadecandiol-2-O-phosphocholine are dissolved in 20 ml of chloroform and 1 ml of dimethylformamide, and 0.5 g of ethyl isocyanate are added. The mixture is stirred at room temperature for 24 hours, the solvent removed and the residue purified by column chromatography (silica gel//chloroform/methanol).
Yield: 1.3 g; Mp: 241°C.

Example 8
1-O-Benzylcarbamoyl-1.2-octadecandiol-2-O-phosphocholine.

2 g of 1.2-octadecandiol-2-O-phosphocholine are dissolved in 20 ml of chloroform and 1 ml of dimethylformamide, and 1.2 g of benzyl isocyanate are added. The mixture is stirred of and the residue is purified by column chromatography (silica gel//chloroform/methanol).
Yield: 1.6 g; Mp: about 211°C (dec.).

Example 9
1-O-Carbamoyl-1.2-octadecandiol-2-O-phosphocholine.

Prepared similarly to 1-O-carbamoyl-1.2-eicosandiol-2-O-phosphocholine, from:
0.5 g of 1-O-benzylcarbamoyl-octadecandiol-2-O-phosphocholine,
50 ml of ethanol and
0.5 g of palladium/active carbon.
Yield: 160 mg; Mp: 236°C (dec.).

Example 10
2-O-Methylcarbamoyl-1.2-octadecandiol-1-O-phosphocholine.

a) 1.2-Octadecandiol-1-O-phosphocholine.
1 g of 2-O-acetyl-1.2-octadecandiol-1-O-phosphocholine are dissolved in 10 ml of absolute ethanol, and 300 mg of potassium carbonate are added. The mixture is stirred at room temperature for 24 hours, filtered and evaporated to dryness in vacuo. The residue (0.8 g) is further processed without purification.

b) 2-O- Methylcarbamoyl-1.2-octadecandiol-1-O-phosphocholine.
0.2 g of 1.2-octadecandiol-1-O-phosphocholine are dissolved in 10 ml of chloroform, and 10 drops of dimethylformamide plus 0.1 g of methyl isocyanate added. The mixture is stirred at room temperature for 48 hours, the solvent removed and the residue purified by column chromatography (silica gel//chloroform/methanol).
Yield: 0.12 g; Mp: 246°C (dec.).

Example 11
2-O-Ethylcarbamoyl-1.2-octadecandiol-1-O-phosphocholine.

0.2 g of 1.2-octadecandiol-1-O-phosphocholine are dissolved in 10 ml of chloroform, and 10 drops of dimethylformamide plus 0.1 g of ethyl isocyanate added. The mixture is stirred at room temperature for 48 hours, the solvent removed and the residue purified by column chromatography (silica gel//chloroform/methanol).
Yield: 0.1 g; Mp: 241°C.

Example 12
1-O-Ethylcarbamoyl-1.2-eicosandiol-2-O-phosphocholine.

a) 1.2-Eicosandiol-2-O-phosphocholine.
2 g of 1-O-acetyl-1.2-eicosandiol-2-O-phosphocholine are dissolved in 20 ml of absolute ethanol, and 530 mg of potassium carbonate added. The mixture is stirred at room temperature for 24 hours, filtered and evaporated to dryness in vacuo. The residue (1.9 g) is further processed without purification.

b) 1-O-Ethylcarbamoyl-1.2-eicosandiol-2-O-phosphocholine.
0.5 g of 1.2-eicosandiol-2-O-phosphocholine are dissolved in 20 ml of chloroform, and 1 ml of dimethylformamide and 0.2 g of ethyl isocyanate added to the solution. The mixture is stirred for about 5 hours at room temperature, the solvent removed and the residue purified by column chromatography (silica gel//chloroform/methanol).
Yield: 0.3 g; Mp: 220°C.

Example 13
1-O-Methylcarbamoyl-1.2-eicosandiol-2-O-phosphocholine.

0.5 g of 1.2-eicosandiol-2-O-phosphocholine are dissolved in 20 ml of chloroform, and 1 ml of dimethylformamide and 0.2 g of methyl isocyanate added to the mixture. The mixture is stirred at room temperature for about 5 hours, the solvent removed and the residue purified by column chromatography (silica gel//chloroform/methanol).
Yield: 0.23 g; Mp: 235°C).

Example 14
1-O-Benzylcarbamoyl-1.2-eicosandiol-2-O-phosphocholine.

0.5 g of 1.2-eicosandiol-2-O-phosphocholine are dissolved in 20 ml of chloroform, and 1 ml of dimethylformamide and 0.5 g of benzyl isocyanate added to the solution. The mixture is stirred at room temperature until reaction is complete, the solvent removed and the residue purified by column chromatography (silica gel//chloroform/methanol).
Yield: 0.5 g; M-: 225°C (dec.).

Example 15
1-O-Carbamoyl-1.2-eicosandiol-2-O-phosphocholine.

0.4 g of 1-O-benzylcarbamoyl-1.2-eicosandiol-2-O-phosphocholine are dissolved in 50 ml of ethanol, the solution hydrogenated with hydrogen for 7 days with successive addition of a total of 0.4 g of palladium/active carbon and a little water. After filtering off the active carbon the filtrate is evaporated to dryness in vacuo, and the residue purified by column chromatography (silica gel//chloroform/metehanol).
Yield: 0.30 g; Mp: 237°C (dec.).

Example 16
3-O-Methylcarbamoyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine.

1 g of 2-octadecyl-1.3-propandiol-1-O-phosphocholine are dissolved in 20 ml of chloroform, and 10 ml of dimethylformamide and 10 ml of methyl isocyanate added to the solution. The mixture is stirred at 60°C until reaction is complete, the solvent removed and the residue purified by column chromatography (silica gel/chloroform/methanol).
Yield: 0.42 g; Mp: 234 to 239°C.

Example 17
3-O-Ethylcarbamoyl-2-octadecyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine.

1 g of 2-octadecyl-1.3-propandiol-1-O-phosphocholine are dissolved in 20 ml of chloroform, and 10 ml of dimethylformamide and 10 ml of ethyl isocyanate added to the solution. The mixture is stirred at 60°C until reaction is complete, the solvent removed and the residue purified by column chromatography (silica gel//chloroform/methanol).
Yield: 0.5 g) Mp: 209 to 218°C.

The following are prepared similarly to examples 6—17:
2-O-methylcarbamoyl-1.2-dodecandiol-1-O-phosphocholine
2-O-ethylcarbamoyl-1.2-dodecandiol-1-O-phosphocholine
2-O-methylcarbamoyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-ethylcarbamoyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-methylcarbamoyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-ethylcarbamoyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-methylcarbamoyl-1.2-eicosandiol-1-O-phosphocholine
2-O-ethylcarbamoyl-1.2-eicosandiol-1-O-phosphocholine
2-O-methylcarbamoyl-1.2-docosandiol-1-O-phosphocholine
2-O-ethylcarbamoyl-1.2-docosandiol-1-O-phosphocholine
1-O-methylcarbamoyl-1.2-dodecandiol-2-O-phosphocholine
1-O-ethylcarbamoyl-1.2-docosandiol-2-O-phosphocholine
1-O-methylcarbamoyl-1.2-tetradecandiol-2-O-phosphocholine
1-O-ethylcarbamoyl-1.2-tetradecandiol-2-O-phosphocholine
1-O-methylcarbamoyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-ethylcarbamoyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-methylcarbamoyl-1.2-docosandiol-2-O-phosphocholine
1-O-ethylcarbamoyl-1.2-docosandiol-2-O-phosphocholine
2-O-phenylcarbamoyl-1.2-eicosandiol-1-O-phosphocholine

2-O-[(4-chlorophenyl)-carbamoyl]-1.2-eicosandiol-1-O-phosphocholine
2-O-hexadecylcarbamoyl-1.2-eicosandiol-1-O-phosphocholine
2-O-oleylcarbamoyl-1.2-eicosandiol-1-O-phoshocholine
2-decyl-3-O-methylcarbamoyl-1.3-propandiol-1-O-phosphocholine
2-dodecyl-3-O-methylcarbamoyl-1.3-propandiol-1-O-phosphocholine
3-O-methylcarbamoyl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
2-hexadecyl-3-O-methylcarbamoyl-1.3-propandiol-1-O-phosphocholine
2-eicosyl-3-O-methylcarbamoyl-1.3-propandiol-1-O-phosphocholine
2-decyl-3-O-methylcarbamoyl-1.3-propandiol-1-O-phosphocholine
2-dodecyl-3-O-methylcarbamoyl-1.3-propandiol-1-O-phosphocholine
3-O-ethylcarbamoyl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
3-O-ethylcarbamoyl-2-hexadecyl-1.3-propandiol-1-O-phosphocholine
2-eicosyl-3-O-ethylcarbamoyl-1.3-propandiol-1-O-phosphocholine.

Example 18
2-O-Dimethylcarbamoyl-1.2-octadecandiol-1-O-phosphocholine.

0.9 g of 1.2-octadecandiol-1-O-phosphocholine are dissolved in 50 ml of chloroform, the solution reacted with 0.43 g of dimethylcarbamic acid chloride and 0.6 g of silver carbonate, and stirred at room temperature for 12 hours. The solution is filtered and evaporated in vacuo and the residue purified by column chromatography (silica gel//chloroform/methanol).
Yield: 0.75 g; Mp: 221°C.

The following are prepared similarly to example 18:
2-O-dimethylcarbamoyl-1.2-dodecandiol-1-O-phosphocholine
2-O-dimethylcarbamoyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-dimethylcarbamoyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-dimethylcarbamoyl-1.2-eicosandiol-1-O-phosphocholine
2-O-dimethylcarbamoyl-1.2-docosandiol-1-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-dodecandiol-2-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-tetradecandiol-2-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-octadecandiol-2-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-eicosandiol-2-O-phosphocholine
1-O-dimethylcarbamoyl-1.2-docosandiol-2-O-phosphocholine
2-decyl-3-O-dimethylcarbamoyl-1.3-propandiol-1-O-phosphocholine
3-O-dimethylcarbamoyl-2-docecyl-1.3-propandiol-1-O-phosphocholine
3-O-dimethylcarbamoyl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
3-O-dimethylcarbamoyl-2-hexadecyl-1.3-propandiol-1-O-phosphocholine
3-O-dimethylcarbamoyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine
3-O-dimethylcarbamoyl-2-eicosyl-1.3-propandiol-1-O-phosphocholine

Example 19
2-O-Ethoxycarbonyl-1.2-eicosandiol-1-O-phosphocholine.

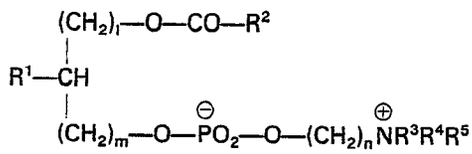
A mixture of 150 mg of 1.2-eicosandiol-1-O-phsophocholine, 70 mg of ethyl chloroformate, 3 drops of triethylamine and 3 ml of chloroform are stirred at 30 to 50°C for 24 hours, the mixture evaporated in vacuo and the residue purified by preparative thin layer chromatography (silica gel//chloroform/methanol/water = 65/35/4).
Yield: 62 mg wax.

The following are prepared similarly to example 19:
2-O-methoxycarbonyl-1.2-dodecandiol-1-O-phosphocholine
2-O-ethoxycarbonyl-1.2-dodecandiol-1-O-phosphocholine
2-O-methoxycarbonyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-ethoxycarbonyl-1.2-tetradecandiol-1-O-phosphocholine
2-O-methoxycarbonyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-ethoxycarbonyl-1.2-hexadecandiol-1-O-phosphocholine
2-O-methoxycarbonyl-1.2-octadecandiol-1-O-phosphocholine
2-O-ethoxycarbonyl-1.2-octadecandiol-1-O-phosphocholine
2-O-methoxycarbonyl-1.2-eicosandiol-1-O-phosphocholine
2-O-methoxycarbonyl-1.2-docosandiol-1-O-phosphocholine
2-O-ethoxycarbonyl-1.2-docosandiol-1-O-phosphocholine
1-O-methoxycarbonyl-1.2-dodecandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-dodecandiol-2-O-phosphocholine

1-O-methoxycarbonyl-1.2-tetradecandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-tetradecandiol-2-O-phosphocholine
1-O-methoxycarbonyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-hexadecandiol-2-O-phosphocholine
1-O-methoxycarbonyl-1.2-octadecandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-octadecandiol-2-O-phosphocholine
1-O-methoxycarbonyl-1.2-eicosandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-eicosandiol-2-O-phosphocholine
1-O-methoxycarbonyl-1.2-docosandiol-2-O-phosphocholine
1-O-ethoxycarbonyl-1.2-docosandiol-2-O-phosphocholine
2-decyl-3-O-methoxycarbonyl-1.3-propandiol-1-O-phosphocholine
2-decyl-3-O-ethoxycarbonyl-1.3-propandiol-1-O-phosphocholine
2-dodecyl-3-O-methoxycarbonyl-1.3-propandiol-1-O-phosphocholine
2-dodecyl-3-O-ethoxycarbonyl-1.3-propandiol-1-O-phosphocholine
3-O-methoxycarbonyl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
3-O-ethoxycarbonyl-2-tetradecyl-1.3-propandiol-1-O-phosphocholine
2-hexadecyl-3-O-methoxycarbonyl-1.3-propandiol-1-O-phosphocholine
3-O-ethoxycarbonyl-2-hexadecyl-1.3-propandiol-1-O-phosphocholine
3-O-methoxycarbonyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine
3-O-ethoxycarbonyl-2-octadecyl-1.3-propandiol-1-O-phosphocholine
2-eicosyl-3-O-methoxycarbonyl-1.3-propandiol-1-O-phosphocholine
2-eicosyl-3-O-ethoxycarbonyl-1.3-propandiol-1-O-phosphocholine

Claims for the Contracting States: BE CH DE FR GB IT LI LU NL SE

1. O-Acyl-alkanediol-phospholipids of the general formula I



wherein R^1 is a straight or branched chain alkyl residue having from 10 to 20 carbon atoms, a straight or branched chain alkenyl group having one double bond and having from 10 to 20 carbon atoms, R^2 is hydrogen, a straight or branched chain alkyl residue having from 1 to 4 carbon atoms, a straight or branched chain alkoxy residue having from 1 to 4 carbon atoms or the group —NR^6R^7, R^3, R^4 and R^5 which may be the same or different from each other, each are hydrogen or an alkyl residue having from 1 to 4 carbon atoms, R^6 and R^7 which may be the same or different from each other, each represent hydrogen, an alkyl residue having from 1 to 20 carbon atoms or an alkenyl group having one double bond and from 1 to 20 carbon atoms, the phenyl group or a phenyl group substituted by C_{1-3}-alkyl, C_{1-3}-alkoxy, halogen or trifluoromethyl, or the benzyl group l and m which may be the same or different from each other, represent 0 or 1 except that l and m may not both be zero, and n represents a whole number from 2 to 4.

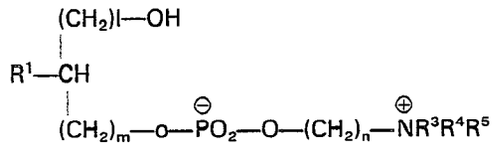
2. O-Acyl-alkanediol-phospholipids as claimed in claim 1, wherein R^2 is hydrogen, a stright chain alkyl residue having from 1 to 4 carbon atoms, a straight chain alkoxy residue having from 1 to 4 carbon atoms or the group —NR^6R^7, R^3, R^4 and R^5 each are a methyl group, R^6 and R^7 are benzyl groups, and n is 2.

3. O-Carbonyl-alkanediol-phospholipids as claimed in claim 1, wherein R^1 is a straight chain or a branched chain alkyl residue having from 10 to 20 carbon atoms, R^2 is —NR^6R^7, R^3, R^4 and R^5 each are a methyl group, R^6 and R^7 which may be the same of different from each other, represent hydrogen, an alkyl residue having from 1 to 20 carbon atoms or an alkenyl group having one double bond and from 1 to 20 carbon atoms, the phenyl group of a phenyl substituted by C_{1-3}-alkyl, C_{1-3}-alkoxy, halogen or trifluoromethyl, or the benzyl residue, l is zero and m is 1.

4. O-Carbamoyl-alkandiol-phospholipids as claimed in claim 1, wherein R^2 is —NR^6R^7, R^3, R^4 and R^5 each are a methyl group, R^6 and R^7 which may be the same or different from each other, are hydrogen, an alkyl residue having from 1 to 20 carbon atoms, an alkenyl group having one double bond and from 1 to 20 carbon atoms, the phenyl group, phenyl substituted by C_{1-3}-alkyl, C_{1-3}-alkoxy, halogen or trifluoromethyl, and the benzyl residue, and l and m both are 1.

5. O-Carbamoyl-alkanediol-phospholipids as claimed in claim 1, wherein R^1 is a straight chain or a branched chain alkyl residue having from 10 to 20 carbon atoms, a straight chain or a branch chain alkenyl group having from 10 to 20 carbon atoms, R^2 is —NR^6R^7, R^3, R^4 and R^5 each are a methyl group, R^6 and R^7 which may be the same or different from each other, are hydrogen, an alkyl residue having from 1 to 20 carbon atoms, an alkenyl group having one double bond and from 1 to 20 carbon atoms, the phenyl group, phenyl substituted by C_{1-3}-alkyl, C_{1-3}-alkoxy, halogen or trifluoromethyl and the benzyl residue, l is 1 and m is zero.

6. Process for the preparation of compounds of the formula I with R′ = H according to claims 1—5, characterized in that lyso-compounds of the general formula II



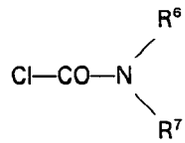
II

in which R^1, R^3, R^4, R^5, l, m and n have the meanings given for formula I, are reacted with an isocyanate of the formula III

III

in which R^6 has the meaning given for formula I, in an aprotic organic solvent with optional addition of a Lewis base as a catalyst.

7. Process for the preparation of compounds of the formula I according to claims 1—5, characterized in that lyso-compounds of the formula II are reacted with the corresponding carbamic acid chloride of the formula IV



IV

in which R^6 and R^7 have the meanings given for formula I, in an inert organic solvent, with optional addition of an acid acceptor.

8. Process for the preparation of compounds of the formula I with $R^6 = R^7 = H$ according to claims 1—5, characterized in that compounds of the formula I with R^6 = benzyl and R^7 = H are hydrogenated in an inert organic solvent in the presence of a conventional hydrogenation catalyst.

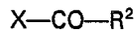
9. O-Alkanoyl-alkandiol-phospholipids of the general formula I, in which R^1 signifies a straight or branched chain alkyl residue with 10 to 20 carbon atoms, R^2 signifies hydrogen or a staight or branched chain alkyl residue with 1—4 carbon atoms, l = 0 and m = 1.

10. O-Alkanoyl-alkandiol-phospholipids of the general formula I, in which R^1 signifies a straight or branched chain alkyl residue with 10 to 20 carbon atoms, R^2 signifies hydrogen or a straight or branched chain alkyl residue with 1—4 carbon atoms, and l = m = 1.

11. O-Alkanoyl-alkandiol-phospholipids of the general formula I, in which R^1 signifies a straight or branched chain alkyl residue with 10 to 20 carbon atoms, R^2 signifies hydrogen or a straight or branched chain alkyl residue with 1—4 carbon atoms, l = 1 and m = 0.

12. O-Alkoxycarbonyl-alkandiol-phospholipids of the general formula I in which R^1 signifies a straight or branched chain alkyl residue with 10 to 20 carbon atoms, R^2 signifies a straight or branched chain alkoxy residue with 1 to 4 carbon atoms and l = 0, m = 1 or l = m = 1, or l, m = 0.

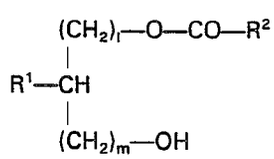
13. Process for the preparation of compounds of the formula I according to claims 9—12, characterized in that lyso-compounds of the general formula II are reacted with the corresponding alkanoic acid halides, alkanoic acid anhydrides or chloroformic acid esters of the formula V



V

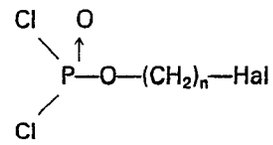
in which X is any halogen, preferably chlorine, or the residue R^2—CO—O— and R^2 is hydrogen or a straight or branched chain alkyl or alkoxy residue according to formula I, in an inert organic solvent, with optional addition of an acid acceptor.

14. Process for the preparation of compounds of the formula I according to claims 1—5, 9—12, characterized in that alcohols of the formula VI



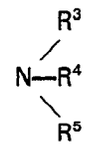
VI

in which R^1, R^2, l, m have the meanings given for formula I, are phosphorylated with a dichlorophosphoric acid ω-haloalkyl ester of the formula VII



VII

in which n has the meaning given for formula I and Hal is a chlorine or bromine atom, in an inert organic solvent, with optional use of an auxiliary base, and further reacted with an amine of the formula VIII



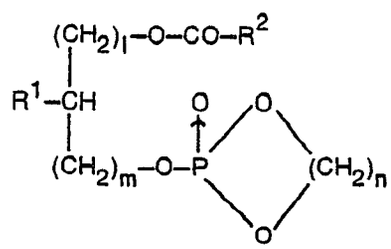
VIII

in which R^3, R^4, R^5 have the meanings given for formula I, in an inert organic solvent, optionally under pressure.

15. Process for the preparation of compounds of the formula I according to claims 1—5, 9—12, characterized in that compounds of the formula VI are phosphorylated with phosphorus oxytrichloride and subsequently reacted with an alkandiol of the formula IX

$$HO—(CH_2)_n—OH \qquad IX$$

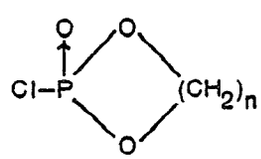
in which n has the meaning given for formula I, with optional use of auxiliary bases and inert solvents, to yield the cyclic phosphorus compounds of the formula X



X

in which R^1, R^2, l, m, n have the meanings given for formula I, and the compounds X are then reacted with an amine of the formula VIII of claim 14, in an organic solvent optionally under pressure.

16. Process for the preparation of compounds of the formula X as defined in claim 15, characterized in that compounds of the formula VI of claim 14 are reacted with a cyclic phosphorus compound of the formula XI



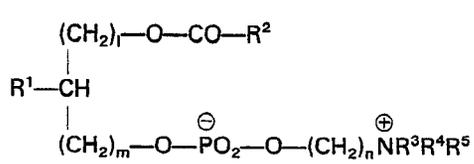
XI

in which n has the meaning given for formula I, in an inert organic solvent with addition of an auxiliary base.

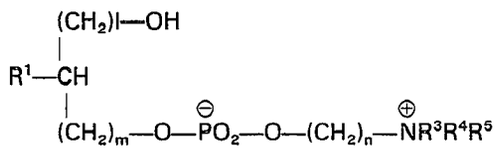
17. Pharmaceutical preparations, characterized in that they contain a compound of the general formula I according to claims 1—5, 9—12 as active ingredient in admixture with conventional pharmaceutical adjuvants and carriers.

Claims for the Contracting State: AT

1. Process for the preparation of compounds of the formula I

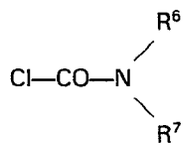


wherein R^1 is a straight or branched chain alkyl residue having from 10 to 20 carbon atoms, a straight or branched chain alkenyl group having one double bond and having from 10 to 20 carbon atoms, R^2 is hydrogen, a straight or branched chain alkyl residue having from 1 to 4 carbon atoms, a straight or branched chain alkoxy residue having from 1 to 4 carbon atoms or the group —NR^6R^7, R^3, R^4 and R^5 which may be the same or different from each other, each are hydrogen or an alkyl residue having from 1 to 4 carbon atoms, R^6 and R^7 which may be the same or different from each other, each represent hydrogen, an alkyl residue having from 1 to 20 carbon atoms or an alkenyl group having one double bond and from 1 to 20 carbon atoms, the phenyl group or a phenyl group substituted by C_{1-3}-alkyl, C_{1-3}-alkoxy, halogen or trifluoromethyl, or the benzyl group l and m which may be the same or different from each other, represent 0 or 1 except that l and m may not both be zero, and n represents a whole number from 2 to 4, characterized in that lyso-compounds of the general formula II



II

in which R^1, R^3, R^4, R^5, l, m and n have the meanings given for formula I, are reacted with the corresponding carbamic acid chlorides of the formula IV



IV

in which R^6 and R^7 have the meanings given for formula I, in an inert organic solvent, with optional addition of an acid acceptor.

2. Process for the preparation of compounds of the formula I as claimed in with R^7 = H, characterised in that lyso-compounds of the general formula II of claim 1 are reacted with an isocyanate of the formula III

$$R^6—N = C = O \qquad \text{III}$$

in which R^6 has the meaning given above for formula I, in an aprotic organic solvent with optional addition of a Lewis base as a catalyst.

3. Process for the preparation of compounds of the formula I as claimed in claim 1 with $R^6 = R^7$ = H, characterised in that compounds of formula I of claim 1 with T^6 = benzyl and R^7 = H are hydrogenated in an organic solvent in the presence of a conventional hydrogenation catalyst.

4. Process for the preparation of compounds of the formula I as claimed in claim 1 wherein R^1 signifies a straight or branched chain alkyl residue with 10 to 20 carbon atoms, R^2 signifies hydrogen or a straight or branched chain alkyl residue with 1 to 4 carbon atoms or a straight or branched chain alkoxy residue with 1 to 4 carbon atoms, R^3, R^4, R^5 which may be the same or different from each other, each are hydrogen or an alkyl residue having from 1 to 4 carbon atoms, l and m which may be the same or different from each other, represent 0 or 1 except that l and m not both be zero, and n represents a whole number from 2 to 4, charactereised in that lyso-compounds of the general formula II of claim 1 wherein R^1, R^3, R^4, R^5, l, m and n have the meanings given above for formula I, are reacted with the corresponding alkanoic acid halides, alkanoic acid anhydrides or chloroformic acid halides, alkanoic acid anhydrides or chloroformic acid esters of the formula V

$$X—CO—R^2 \qquad \text{V}$$

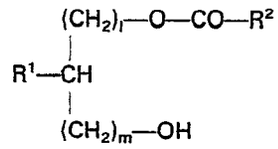
wherein X is any halogen, preferably chlorine, or the residue R^2—CO—O— and R^2 has the meaning given above for formula I of claim 1 in an inert organic solvent, with optional addition of an acid acceptor.

5. Process for the preparation of compounds of the formula I as claimed in claim 1 wherein R^1, R^2, R^3, R^4, R^5, l, m and n have the meanings given in claim 4 for formula I, characterised in that lyso-compounds of the general formula II in which R^1, R^3, R^4, R^5, l, m and n have the meanings given above for formula I, are reacted with an isocyanate of the formula III

$$R^6—N = C = O \qquad \text{III}$$

in which R^6 has the meaning given above for formula I, in an aprotic organic solvent with optional addition of a Lewis base as a catalyst.

6. Process for the preparation of compounds of the formula I as claimed in claim 1 wherein R^1, R^2, R^3, R^4, R^5, l, m and n have the meanings given in claim 4 for formula I, characterized in that compounds of the formula VI

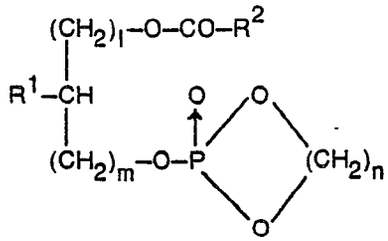


VI

wherein R^1, R^2, l and m have the meanings given above for formula I, are phosphorylated with phosphorus oxytrichloride and subsequently reacted with an alkanediol of the formula IX

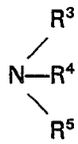
$$HO—(CH_2)_n—OH \qquad IX$$

wherein n has the meaning given above for formula I, with optional use of auxiliary bases and inert solvents, to yield the cyclic phosphorus compounds of the formula X



X

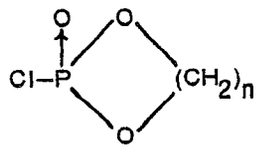
wherein R^1, R^2, l, m, n have the meanings given above for formula I, and the compounds X are then reacted with an amine of the formula VIII



VIII

wherein n has the meanings given above for formula I, in an organic solvent optionally under pressure.

7. Process for the preparation of compounds of formula X as claimed in claim 6, characterised in that the compounds of formula VI of claim 5 are reacted with a cyclic phosphorus compound of the formula XI

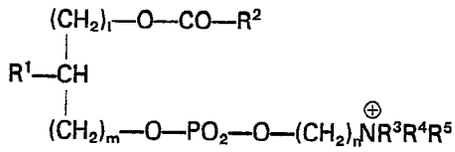


XI

wherein n has the meaning given above for formula I, in an inert organic solvent with addition of an auxiliary base.

Patentansprüche für die Vertragsstaaten BE CH DE FR GB IT LI LU NL SE:

1. O-Acyl-alkandiol-phospholipide der allgemeinen Formel I



I

worin R^1 ein geradkettiger oder verzweigter Alkylrest mit 10—20 Kohlenstoffatomen, ein geradkettiger oder verzweigter Alkenylrest mit einer Doppelbindung und 10—20 Kohlenstoffatomen, R^2 Wasserstoff, ein geradkettiger oder verzweigter Alkylrest mit 1—4 Kohlenstoffatomen, ein geradkettiger oder verzweigter Alkoxyrest mit 1—4 Kohlenstoffatomen oder die Gruppe NR^6R^7 ist, R^3, R^4 und R^5, die gleich oder voneinander verschieden sein können, jeweils Wasserstoff oder einen Alkylrest mit 1—4 Kohlenstoffatomen sind, R^6 und R^7, die gleich oder voneinander verschieden sein können, jeweils Wasserstoff, einen Alkylrest mit 1—20 Kohlenstoffatomen oder einen Alkenylrest mit einer Doppelbindung

und 1—20 Kohlenstoffatomen, die Phenylgruppe oder eine mit C_{1-3}-Alkyl, C_{1-3}-Alkoxy, Halogen oder Trifluormethyl substituierte Phenylgruppe oder die Benzylgruppe ist, 1 und m, die gleich oder voneinander verschieden sein können, 0 oder 1 bedeuten, mit der Ausnahme, daß 1 und m nicht beide 0 sein können, und n eine ganze Zahl von 2—4 darstellt.

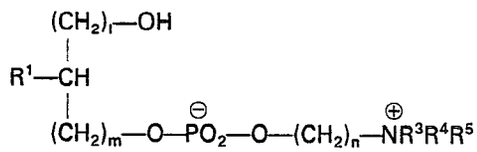
2. O-Acyl-alkandiol-phospholipide gemäß Anspruch 1, worin R^2 Wasserstoff, einen geradkettigen Alkylrest mit 1—4 Kohlenstoffatomen, einen geradkettigen Alkoxyrest mit 1—4 Kohlenstoffatomen oder die Gruppe —NR^6R^7 ist, R^3, R^4 und R^5 jeweils eine Methylgruppe, R^6 und R^7 Benzylgruppen sind und n 2 ist.

3. O-Carbamoyl-alkandiol-phospholipide gemäß Anspruch 1, worin R^1 eine geradkettige oder verzweigte Alkylgruppe mit 10 bis 20 Kohlenstoffatomen, R^2 —NR^6R^7 ist, R^3, R^4 und R^5 jeweils eine Methylgruppe darstellen, R^6 und R^7, die gleich oder voneinander verschieden sein können, Wasserstoff, einen Alkylrest mit 1—20 Kohlenstoffatomen oder einen Alkenylrest mit einer Doppelbindung und 1—20 Kohlenstoffatomen, die Phenylgruppe oder eine durch C_{1-3}-Alkyl, C_{1-3}-Alkoxy, Halogen oder Trifluormethyl substituierte Phenylgruppe oder der Benzylrest ist, 1 0 und m 1 ist.

4. O-Carbamoyl-alkandiol-phospholipide gemäß Anspruch 1, worin R^2 —NR^6R^7 ist, R^3, R^4 und R^5 jeweils eine Methylgruppe sind, R^6 und R^7, die gleich oder voneinander verschieden sein können, Wasserstoff, eine alkylgruppe mit 1 bis 20 Kohlenstoffatomen, eine Alkenylgruppe mit einer Doppelbindung und 1 bis 20 Kohlenstoffatomen, die Phenylgruppe, durch C_{1-3}-Alkyl, C_{1-3}-Alkoxy, Halogen oder Trifluormethyl substituiertes Phenyl oder die Benzylgruppe und 1 und m beide 1 sind.

5. O-Carbamoyl-alkandiol-phospholipide gemäß Anspruch 1, worin R^1 ein geradkettiger oder verzweigter Alkylrest mit 10 bis 20 Kohlenstoffatomen, ein geradkettiger oder verzweigter Alkenylrest mit 10 bis 20 Kohlenstoffatomen, R^2 —NR^6R^7 ist, R^3, R^4 und R^5 jeweils eine Methylgruppe sind, R^6 und R^7, die gleich oder voneinander verschieden sein können, Wasserstoff, einen Alkylrest mit 1—20 Kohlenstoffatomen, eine Alkenylgruppe mit einer Doppelbindung und 1—20 Kohlenstoffatomen, die Phenylgruppe, durch C_{1-3}-Alkyl, C_{1-3}-Alkoxy, Halogen oder Trifluormethyl substituiertes Phenyl oder die Benzylgruppe sind, l 1 und m 0 ist.

6. Verfahren zur Herstellung von Verbindungen der Formel I mit R^7 = H gemäß Ansprüchen 1—5, dadurch gekennzeichnet, daß Lyso-Verbindungen der allgemeinen Formel II

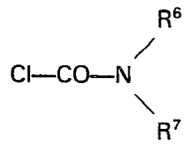


worin R^1, R^3, R^4, R^5, l, m und n die für Formel I angegebene Bedeutung haben, mit einem Isocyanat der Formel III

$$R^6—N=C=O \qquad \text{III}$$

worin R^6 die für Formel I angegebene Bedeutung hat, in einem aprotischen organischen Lösungsmittel, gegebenenfalls unter Zugabe einer Lewis-Base als Katalysator umgesetzt werden.

7. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Ansprüchen 1—5, dadurch gekennzeichnet, daß Lyso-Verbindungen der Formel II mit den entsprechenden Carbaminsäurechloriden der Formel IV



IV

worin R^6 und R^7 die für Formel I angegebene Bedeutung haben, in einem inerten organischen Lösungsmittel, gegebenenfalls unter Zugabe eines Säurefängers zugesetzt werden.

8. Verfahren zur Herstellung von Verbindungen der Formel I mit R^6=R^7=H gemäß Ansprüchen 1—5, dadurch gekennzeichnet, daß Verbindungen der Formel I mit R^6 = Benzyl und R^7 = H in einem organischen Lösungsmittel in Anwesenheit eines üblichen Hydrierungskatalysators hydriert werden.

9. O-Alkanoyl-alkandiol-phospholipide der allgemeinen Formel I, worin R^1 einen geradkettigen oder verzweigten Alkylrest mit 10—20 Kohlenstoffatomen, R^2 Wasserstoff oder einen geradkettigen oder verzweigten Alkylrest mit 1—4 Kohlenstoffatomen bedeutet, 1 = 0 und m = 1 ist.

10. O-Alkanoyl-alkandiol-phospholipide der allgemeinen Formel I, worin R^1 einen geradkettigen oder verzweigten Alkylrest mit 10—20 Kohlenstoffatomen, R^2 Wasserstoff oder einen geradkettigen oder verzweigten Alkylrest mit 1—4 Kohlenstoffatomen bedeutet, und l = m = 1 ist.

11. O-Alkanoyl-alkandiol-phospholipide der allgemeinen Formel I, worin R^2 einen geradkettigen oder verzweigten Alkylrest mit 10—20 Kohlenstoffatomen, R^2 Wasserstoff oder einen geradkettigen oder verzweigten Alkylrest mit 1—4 Kohlenstoffatomen bedeutet, und l = 1 und m = 0 ist.

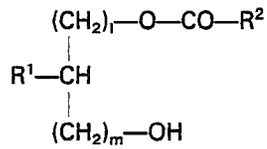
12. O-Alkoxycarbonyl-alkandiol-phospholipide der allgemeinen Formel I, worin R^1 einen geradkettigen oder verzweigten Alkylrest mit 10—20 Kohlenstoffatomen, R^2 einen geradkettigen oder verzweigten Alkoxyrest mit 1—4 Kohlenstoffatomen und l = 0, m = 1 oder l = m = 1 oder l = 1 bei m = 0 ist.

13. Verfahren zur Herstellung der Verbindungen der allgemeinen Formel I gemäß Ansprüchen 9—12, dadurch gekennzeichnet, daß Lyso-Verbindungen der allgemeinen Formel II mit den entsprechenden Alkansäurehalogeniden, Alkansäureanhydriden oder Chlorameisensäureestern der Formel V

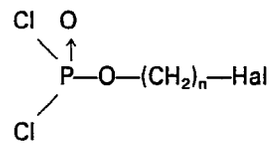
$$X—CO—R^2 \qquad V$$

worin X irgendein Halogen, vorzugsweise Chlor, oder der Rest R^2—CO—O— und R^2 Wasserstoff oder ein geradkettiger oder verzweigter Alkyl- oder Alkoxyrest gemäß Formel I ist, in einem inerten organischen Lösungsmittel, gegebenenfalls in Anwesenheit eines Säurefängers, umgesetzt wird.

14. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Ansprüchen 1—5 und 9—12, dadurch gekennzeichnet, daß Alkohole der Formel VI

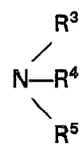


worin R^1, R^2, l, m die für Formel I angegebene Bedeutung haben, mit einem Dichlorphosphorsäure-ω-halogenalkylester der Formel VII



VII

worin n die für Formel I angegebene Bedeutung hat und Hal ein Chlor- oder Bromatom ist, in einem inerten organischen Lösungsmittel, gegebenenfalls in Anwesenheit einer Hilfsbase, umgesetzt werden und sodann weiter mit einem Amin der Formel VIII



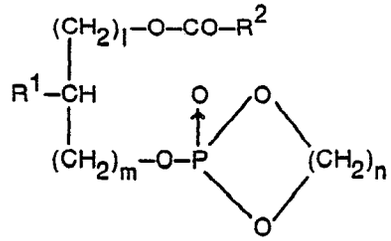
VIII

worin R^3, R^4 und R^5 die für Formel I angegebene Bedeutung haben, in einem inerten organischen Lösungsmittel, gegebenenfalls unter Druck, umgesetzt werden.

15. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Ansprüchen 1—5 und 9—12, dadurch gekennzeichnet, daß Verbindungen der Formel VI mit Phosphoroxytrichlorid phosphoryliert werden und nachfolgend mit einem Alkandiol der Formel IX

$$HO—(CH_2)_n—OH \qquad IX$$

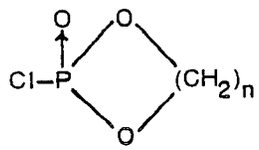
worin n die für Formel I angegebene Bedeutung haben, gegebenenfalls in Anwesenheit von Hilfsbasen und inerten Lösungsmitteln zu cyclischen Phosphorverbindungen der Formel X



X

worin R^1, R^2, l, m und n die für Formel I angegebenen Bedeutungen haben,
umgesetzt werden und die Verbindungen der Formel X sodann mit einem Amin der Formel VIII gemäß Anspruch 14 in einem organischen Lösungsmittel gegebenenfalls unter Druck umgesetzt werden.

16. Verfahren zur Herstellung von Verbindungen der Formel X gemäß Anspruch 15, dadurch gekennzeichnet, daß Verbindungen der Formel VI gemäß Anspruch 14 mit einer cyclischen Phosphorverbindung der Formel XI



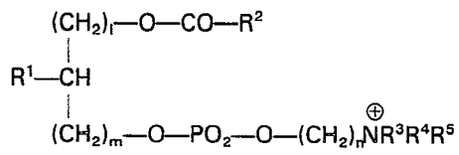
XI

worin n die für Formel I angegebene Bedeutung hat, in einem inerten organischen Lösungsmittel unter Zugabe einer Hilfsbase umgesetzt werden.

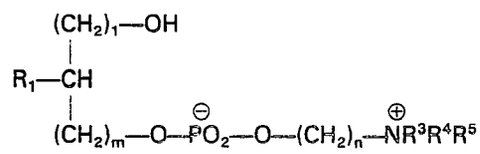
17. Pharmazeutische Zubereitungen, dadurch gekennzeichnet, daß sie eine Verbindung der allgemeinen Formel I gemäß Ansprüchen 1—5 und 9—12 als Wirkstoff zusätzlich zu üblichen pharmazeutischen Zusatzstoffen und Trägerstoffen enthalten.

Patentansprüche für Vertragsstaat AT:

1. Verfahren zur Herstellung von Verbindungen der Formel I

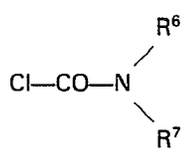


worin R^1 ein geradkettiger oder verzweigter Alkylrest mit 10 bis 20 Kohlenstoffatomen, ein geradkettiger oder verzweigter Alkenylrest mit einer Doppelbindung und 10 bis 20 Kohlenstoffatomen, R^2 Wasserstoff, ein geradkettiger oder verzweigter Alkylrest mit 1 bis 4 Kohlenstoffatomen, ein geradkettiger oder verzweigter Alkoxyrest mit 1 bis 4 Kohlenstoffatomen oder die Gruppe NR^6R^7 ist, R^3, R^4 und R^5, die gleich oder voneinander verschieden sein können, jeweils Wasserstoff oder einen Alkylrest mit 1 bis 4 Kohlenstoffatomen sind, R^6 und R^7, die gleich oder voneinander verschieden sein können, jeweils Wasserstoff, einen Alkylgruppe mit 1 bis 20 Kohlenstoffatomen oder eine Alkenylgruppe mit einer Doppelbindung und 1 bis 20 Kohlenstoffatomen, die unsubstituierte oder durch C_{1-3}-Alkyl, C_{1-3}-Alkoxy, Halogen oder Trifluormethyl substituierte Phenylgruppe oder die Benzylgruppe sind, l und m, die gleich oder voneinander verschieden sein können, 0 oder 1 darstellen, mit der Ausnahme, daß l und m nicht beide Null sein können, und n eine ganze Zahl von 2 bis 4 bedeutet, dadurch gekennzeichnet, daß Lyso-Verbindungen der Formel II



II

worin R^1, R^3, R^4, R^5, l, m und n die für Formel I angegebene Bedeutung haben, mit den entsprechenden Carbaminsäurechloriden der Formel IV



IV

worin R^6 und R^7 die für Formel I angegebenen Bedeutung haben, in einem inerten organischen Lösungsmittel, gegebenenfalls unter Zugabe eines Säureempfängers, umgesetzt werden.

2. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Anspruch 1 mit R^7 = H, dadurch gekennzeichnet, daß Lyso-Verbindungen der allgemeinen Formel II aus Anspruch 1 mit einem Isocyanat der Formel III

$$R^6—N=C=O \qquad \text{III}$$

worin R^6 die wie oben für Formel I angegebene Bedeutung hat, in einem aprotischen organischen Lösungsmittel, gegebenenfalls unter Zugabe einer Lewis-Base als Katalysator umgesetzt werden.

3. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Anspruch 1 mit R^6=R^7=H, dadurch

gekennzeichnet, daß Verbindungen der Formel I gemäß Anspruch 1 mit R^6 = Benzyl und R^7 = H in einem organischen Lösungsmittel in Anwesenheit eines üblichen Hydrierungskatalysators hydriert werden.

4. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Anspruch 1, worin R^1 ein geradkettiger oder verzweigter Alkylrest mit 10 bis 20 Kohlenstoffatomen, R^2 Wasserstoff oder ein geradkettiger oder verzweigter Alkylrest mit 1 bis 4 Kohlenstoffatomen oder ein geradkettiger oder verzweigter Alkoxyrest mit 1 bis 4 Kohlenstoffatomen ist, R^3, R^4 und R^5, die gleich oder voneinander verschieden sein können, jeweils Wasserstoff oder einen Alkylrest mit 1 bis 4 Kohlenstoffatomen bedeuten, l und m, die gleich oder voneinander verschieden sein können, 0 oder 1 mit der Ausnahme darstellen, daß l und m nicht beide Null sein können, und n eine ganze Zahl von 2 bis 4 bedeuten, dadurch gekennzeichnet, daß Lyso-Verbindungen der allgemeinen Formel II des Anspruches 1, worin R^1, R^3, R^4, R^5, l, m und n die oben angegebene Bedeutung für Formel I haben, mit den entsprechenden Alkansäurehalogeniden, Alkansäureanhydriden oder Chloressigsäureestern der Formel V

$$X—CO—R^2 \qquad V$$

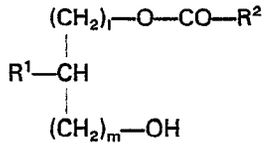
worin X irgendein Halogenatom, vorzugsweise Chlor, oder der Rest R^2—CO—O— ist und R^2 die oben für Formel I des Anspruches 1 angegebene Bedeutung hat, in einem inerten organischen Lösungsmittel, wie gegebenenfalls in Anwesenheit eines Säurefängers, umgesetzt werden.

5. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Anspruch 1, worin R^1, R^2, R^3, R^4, R^5, l, m und n die für Formel I im Anspruch 4 angegebene Bedeutung haben, dadurch gekennzeichnet, daß Lyso-Verbindungen der allgemeinen Formel II, worin R^1, R^3, R^4, R^5, l, m und n die oben für Formel I angegebene Bedeutung haben, mit einem Isocyanat der Formel III

$$R^6—N=C=O \qquad III$$

worin R^6 die oben für Formel I angegebene Bedeutung hat, in einem aprotischen organischen Lösungsmittel, gegebenenfalls unter Zugabe einer Lewis-Base als Katalysator umgesetzt werden.

6. Verfahren zur Herstellung von Verbindungen der Formel I gemäß Anspruch 1, worin R^1, R^2, R^3, R^4, R^5, l, m und n die für Formel I in Anspruch 4 angegebene Bedeutung haben, dadurch gekennzeichnet, daß Verbindungen der Formel VI

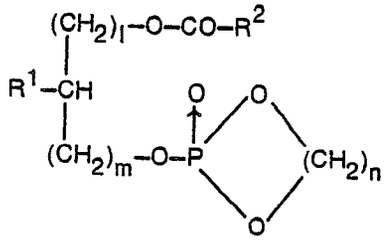


VI

worin R^1, R^2, l und m die oben für Formel I angegebene Bedeutung haben, mit Phosphoroxychlorid phosphoryliert und nachfolgend mit einem Alkandiol der Formel IX

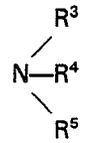
$$HO—(CH_2)_n—OH \qquad IX$$

worin n die oben für Formel I angegebene Bedeutung hat, gegebenenfalls unter Zugabe von Hilfsbasen und inerten organischen Lösungsmitteln zu den cyclischen Phosphorverbindungen der Formel X umgesetzt werden,



X

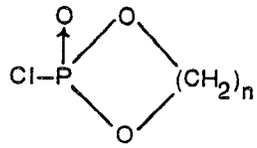
worin R^1, R^2, l, m und n die oben für Formel I angegebene Bedeutung haben, sodann mit einem Amin der Formel VIII



VIII

worin n die oben für Formel I angegebene Bedeutung hat, in einem organischen Lösungsmittel, gegebenenfalls unter Druck, umgesetzt werden.

7. Verfahren zur Herstellung von Verbindungen der Formel X gemäß Anspruch 6, dadurch gekennzeichnet, daß Verbindungen der Formel VI gemäß Anspruch 5 mit einer cyclischen Phosphorverbindung der Formel XI

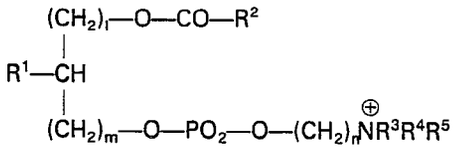


XI

worin n die oben für Formel I angegebene Bedeutung hat, in einem inerten organischen Lösungsmitel unter Zugabe einer Hilfsbase umgesetzt werden.

Revendications pour les Etats contractants BE CH DE FR GB IT LI LU NL SE:

1. O-acyl-alcanediol-phospholipides de formule générale I:



dans laquelle R^1 est un reste alkyle à chaîne droite ou ramifiée, contenant 10 à 20 atomes de carbone, un groupe alcényle à chaîne droite ou ramifiée comportant une double liaison et contenant de 10 à 20 atomes de carbone, R^2 est un atome d'hydrogène, un reste alkyle à chaîne droite ou ramifiée contenant 1 à 4 atomes de carbone, un reste alcoxy à chaîne droite ou ramifiée contenant de 1 à 4 atomes de carbone ou le groupe —NR^6R^7, R^3, R^4 et R^5, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un reste alkyle contenant 1 à 4 atomes de carbone, R^6 et R^7, qui peuvent être identiques ou différents représentent chacun un atome d'hydrogène, un radical alkyle de 1 à 20 atomes de carbone ou un radical alcényle comportant une double liaison et contenant 1 à 20 atomes de carbone, le radical phényle ou un radical phényle substitué par un alkyle en C_{1-3}, alcoxy en C_{1-3}, halogène ou trifluorométhyle, ou bien le groupe benzyle, *l* et *m* qui peuvent être identiques ou différents représentent chacun 0 ou 1 sauf que *l* et *m* ne peuvent pas être simultanément 0 et *n* est un nombre entier de 2 à 4.

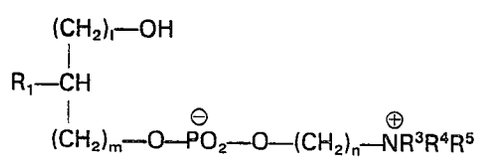
2. O-acyl-alcanediol-phospholipides selon la revendication 1, dans lesquels R^2 est un atome d'hydrogène, un reste alkyle à chaîne droite de 1 à 4 atomes de carbone, un reste alcoxy à chaîne droite de 1 à 4 atomes de carbone ou le groupe —NR^6R^7, R^3, R^4 et R^5 représentent chacun un radical méthyle, R^6 et R^7 représentent des radicaux benzyle et *n* est 2.

3. O-carbamoyl-alcanediol-phospholipides selon la revendication 1, dans lesquels R^1 est un reste alkyle à chaîne droite ou ramifiée contenant 10 à 20 atomes de carbone, R^2 représente —NR^6R^7, R^3, R^4 et R^5 représentent chacun un radical méthyle, R^6 et R^7, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un reste alkyle de 1 à 20 atomes de carbone, ou un radical alcényle comportant une double liaison et contenant de 1 à 20 atomes de carbone, le radical phényle ou un phényle substitué par alkyle en C_{1-3}, alcoxy en C_{1-3}, halogène, ou trifluorométhyle, ou le reste benzyle, *l* est zéro et *m* est 1.

4. O-carmamoyl-alcanediol-phospholipides selon la revendication 1, dans lesquels R^2 représente —NR^6R^7, R^3, R^4 et R^5 représentent chacun un radical méthyle, R^6 et R^7 qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un reste alkyle de 1 à 20 atomes de carbone, un radical alcényle comportant une double liaison et contenant de 1 à 20 atomes de carbone, le radical phényle ou un phényle substitué par alkyle en C_{1-3}, alcoxy en C_{1-3}, halogène ou trifluorométhyle et un reste benzyle, et *l* et *m* sont tous deux 1.

5. O-carbamoyl-alcanediol-phospholipides selon la revendication 1, dans lesquels R^1 est un reste alkyle a chaîne droite ou ramifiée de 10 à 20 atomes de carbone, un radical alcényle à chaîne droite ou ramifiée de 10 à 20 atomes de carbone, R^2 représente —NR^6R^7, R^3, R^4, et R^5 représentent chacun un radical méthyle, R^6 et R^7 qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène, un reste alkyle de 1 à 20 atomes de carbone, un radical alcényle comportant une double liaison et contenant de 1 à 20 atomes de carbone, le radical phényle ou un phényle substitué par alkyle en C_{1-3}, alcoxy en C_{1-3}, halogène ou trifluorométhyle et le reste benzyle, *l* est 1 et *m* est 0.

6. Procédé de préparation de composés de formule I dans laquelle R^7 = H selon les revendications 1 à 5, caractérisé en ce qu'on fait réagir les composés lyso de formule générale II



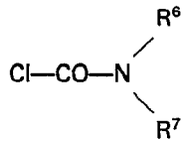
II

dans laquelle R^1, R^3, R^4, R^5, *l*, *m* et *n* ont les significations données pour la formule I avec un isocyanate de formule III:

$$R^6—N=C=O \qquad \text{III}$$

dans laquelle R^6 a la signification donnée pour la formule I au sein d'un solvant organique aprotique avec addition facultative d'une base de Lewis comme catalyseur.

7. Procédé de préparation de composés de formule I selon les revendications 1 à 5, caractérisé en ce qu'on fait réagir les composés lyso de formule II avec les chlorures d'acide carbamique correspondants de formule IV:



IV

dans laquelle R^6 et R^7 ont les significations données pour la formule I, au sein d'un solvant organique inerte avec addition facultative d'un accepteur d'acides.

8. Procédé de préparation de composés de formule I dans laquelle $R^6 = R^7 = H$ selon les revendications 1 à 5, caractérisé en ce qu'on hydrogène les composés de formule I dans laquelle R^6 = benzyle et $R^7 = H$ au sein d'un solvant organique inerte en présence d'un catalyseur classique d'hydrogénation.

9. O-alcanoyl-alcanediol-phospholipides de formule générale I, dans laquelle R^1 désigne un reste alkyle à chaîne droite ou ramifiée de 10 à 20 atomes de carbone, R^2 est un atome d'hydrogène ou un reste alkyle à chaîne droite ou ramifiée de 1 à 4 atomes de carbone, *l* = zéro et *m* = 1.

10. O-alcanoyl-alcanediol-phospholipides de formule générale I dans laquelle R^1 est un reste alkyle à chaîne droite ou ramifiée de 10 à 20 atomes de carbone, R^2 est un atome d'hydrogène ou un reste alkyle à chaîne droite ou ramifiée de 1 à 4 atomes de carbone et *l* = *m* = 1.

11. O-alcanoyl-alcanediol-phospholipides de formule générale I dans laquelle R^1 est un reste alkyle à chaîne droite ou ramifiée de 10 à 20 atomes de carbone, R^2 est un atome d'hydrogène ou un reste alkyle à chaîne droite ou ramifiée de 1 à 4 atomes de carbone, *l* = 1 et *m* = 0.

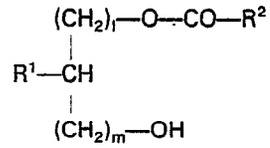
12. O-alcoxycarbonyl-alcanediol-phospholipides de formule générale I dans laquelle R^1 est un reste alkyle à chaîne droite ou ramifiée de 10 à 20 atomes de carbone, R^2 est un reste alcoxy à chaîne droite ou ramifiée de 1 à 4 atomes de carbone et *l* = 0, *m* = 1 ou *l* = *m* = 1 ou *l* = 1, *m* = 0.

13. Procédé de préparation de composés de formule I selon les revendications 9 à 12, caractérisé en ce qu'on fait réagir les composés lyso de formule générale II avec les halogénures d'acide alcanoïque correspondants, les anhydrides d'acide alcanoïque ou les esters d'acide chloroformique de formule V:

$$X—CO—R^2 \qquad \text{V}$$

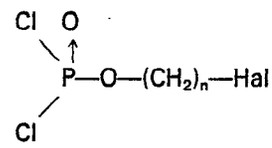
dans laquelle X est un halogène quelconque, de préférence le chlore ou le résidu R^2—CO—O— et R^2 est un atome d'hydrogène ou un reste alkyle ou alcoxy à chaîne droite ou ramifiée selon la formule I, dans un solvant organique inerte avec addition facultative d'un accepteur d'acides.

14. Procédé de préparation de composés de formule I selon les revendications 1 à 5 ou 9 à 12, caractérisé en ce qu'on soumet à une phosphorylation des alcools de formule VI:



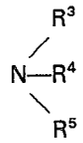
VI

dans laquelle R^1, R^2, *l* et *m* ont les significations données pour la formule I, avec l'esters w-haloalkylique d'acide dichlorophosphorique de formule VII:



VII

dans laquelle *n* a la signification donnée pour la formule I et Hal représente un atome de chlore ou de brome, dans un solvant organique inerte, avec utilisation facultative d'une base auxiliaire et on fait ensuite réagir avec une amine de formule VIII:



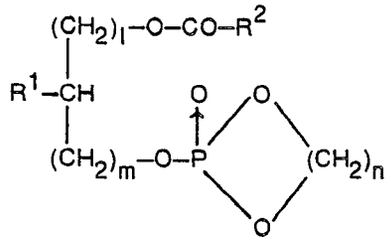
VIII

dans laquelle R^3, R^4 et R^5 ont les significations données pour la formule I, dans un solvant organique inerte facultativement sous pression.

15. Procédé de préparation de composés de formule I selon les revendications 1 à 5 ou 9 à 12, caractérisé en ce qu'on soumet à une phosphorylation les composés de formule VI avec l'oxytrichlorure de phosphore et qu'ensuite en fait réagir avec un alcanediol de formule IX:

$$HO(CH_2)_n—OH \qquad IX$$

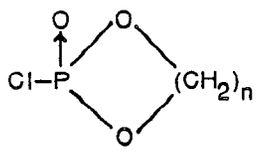
dans laquelle *n* a la signification donnée pour la formule I avec emploi facultatif des bases auxiliaires et de solvants inertes, pour obtenir les composés cycliques de phosphore de formule X:



X

dans laquelle R^1, R^2, *l*, *m* et *n* ont les significations données pour la formule I et ensuite on fait réagir les composés X avec une amine de formule VIII selon la revendication 14 dans un solvant organique facultativement sous pression.

16. Procédé de préparation de composés de formule X tels que définis selon la revendication 15, caractérisé en ce qu'on fait réagir les composés de formule VI selon la revendication 14 avec un composé cyclique de phosphore de formule XI:



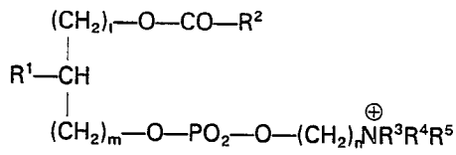
XI

dans laquelle *n* est tel que défini pour la formule I au sein d'un solvant organique inerte avec addition d'une base auxiliaire.

17. Compositions pharmaceutiques, caractérisées en ce qu'elles contiennent un composé de formule générale I selon les revendications 1 à 5 ou 9 à 12 à titre d'ingrédient actif en mélange avec des adjuvants et véhicules pharmaceutiques classiques.

Revendications pour l'Etat contractant AT:

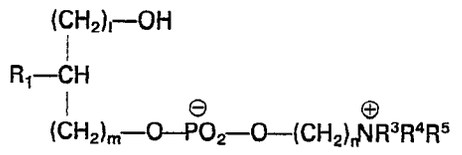
1. Procédé de préparation de composés de formule I:



I

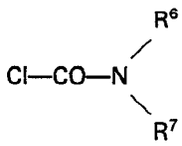
dans laquelle R^1 est un reste alkyle à chaîne droite ou ramifiée, contenant 10 à 20 atomes de carbone, un groupe alcényle à chaîne droite ou ramifiée comportant une double liaison et contenant de 10 à 20 atomes de carbone, R^2 est un atome d'hydrogène, un reste alkyle à chaîne droite ou ramifiée contenant 1 à 4 atomes de carbone, un reste alcoxy à chaîne droite ou ramifiée contenant de 1 à 4 atomes de carbone ou le groupe $—NR^6R^7$, R^3, R^4 et R^5, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un reste alkyle contenant 1 à 4 atomes de carbone, R^6 et R^7, qui peuvent être identiques ou différents représentent chacun un atome d'hydrogène, un radical alkyle de 1 à 20 atomes de carbone ou un radical alcényle comportant une double liaison et contenant 1 à 20 atomes de carbone, le radical phényle ou un radical phényle substitué par un alkyle en C_{1-3}, alcoxy en C_{1-3}, halogéne ou trifluorométhyle, ou bien

le groupe benzyle, *l* et *m* qui peuvent être identiques ou différents représentent chacun 0 ou 1 sauf que *l* et *m* ne peuvent pas être simultanément 0 et *n* est un nombre entier de 2 à 4, caractérisé en ce qu'on fait réagir les composés lyso de formule générale II:



II

dans laquelle R^1, R^3, R^4, R^5, *l*, *m* et *n* ont les mêmes significations que dans la formule I, avec les chlorures d'acide carbamique correspondants de formule IV:



IV

dans laquelle R^6 et R^7 ont les mêmes significations que pour la formule I, dans un solvant organique inerte avec addition facultative d'un accepteur d'acides.

2. Procédé de préparation de composés de formule I selon la revendication 1, dans laquelle R^7 = H, caractérisé en ce qu'on fait réagir les composés lyso de formule générale II selon la revendication 1, avec un isocyanate de formule III:

$$R^6—N=C=O \qquad \text{III}$$

dans laquelle R^6 a la signification donnée ci-dessus pour la formule I au sein d'un solvant organique aprotique avec addition facultative d'une base de Lewis comme catalyseur.

3. Procédé de préparation de composés de formule I selon la revendication 1, dans laquelle $R^6 = R^7 =$ H, caractérisé en ce qu'on hydrogène les composés de formule I selon la revendication 1 dans laquelle R^6 = benzyle et R^7 = H dans un solvant organique en présence d'un catalyseur classique d'hydrogénation.

4. Procédé de préparation de composés de formule I selon la revendication 1, dans laquelle R^1 est un reste alkyle à chaîne droite ou ramifiée de 10 à 20 atomes de carbone, R^2 est un atome d'hydrogène ou un reste alkyle à chaîne droite ou ramifiée de 1 à 4 atomes de carbone ou un reste alcoxy à chaîne droite ou ramifiée de 1 à 4 atomes de carbone, R^3, R^4 et R^5, qui peuvent être identiques ou différents, représentent chacun un atome d'hydrogène ou un reste alkyle de 1 à 4 atomes de carbone, *l* et *m* qui peuvent être identiques ou différents représentent 0 ou 1 sauf que *l* et *m* ne peuvent pas tous deux être 0 et *n* est un nombre entier de 2 à 4, caractérisé en ce qu'on fait réagir les composés lyso de formule générale II selon la revendication 1 dans laquelle R^1, R^3, R^4, R^5, *l* et *n* ont les significations données ci-dessus dans la formule I, avec les halogénures d'acide alcanoïque correspondants, les anhydrides d'acide alcanoïque ou les halogénures d'acide chloroformique, les anhydrides d'acide alcanïque ou les esters d'acide chloroformique de formule V:

$$X—CO—R^2 \qquad \text{V}$$

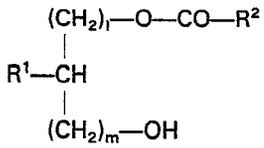
dans laquelle X est un halogène quelconque, de préférence le chlore ou le résidu R^2—CO—O— et R^2 a la significations donnée ci-dessus pour la formule I selon la revendication 1 au sein d'un solvant organique inerte avec addition facultative d'un accepteur d'acides.

5. Procédé de préparation de composés de formule I selon la revendication 1, dans laquelle R^1, R^2, R^3, R^4, R^5, *l*, *m* et *n* ont les significations indiquées dans la revendication 4 pour la formule I, caractérisé en ce qu'on fait réagir les composés lyso de formule générale II dans laquelle R^1, R^3, R^4, R^5, *l*, *m* et *n* ont les significations données pour la formule I ci-dessus, avec un isocyanate de formule III:

$$R^6—N=C=O \qquad \text{III}$$

dans laquelle R^6 est tel que défini ci-dessus pour la formule I, au sein d'un solvant organique aprotique avec addition facultative d'une base de Lewis comme catalyseur.

6. Procédé de préparation de composés de formule I selon la revendication 1, dans laquelle R^1, R^2, R^3, R^4, R^5, *l*, *m* et *n* ont les mêmes significations que dans la revendication 4 pour la formule I, caractérisé en ce qu'on soumet à une phosphorylation les composés de formule VI:

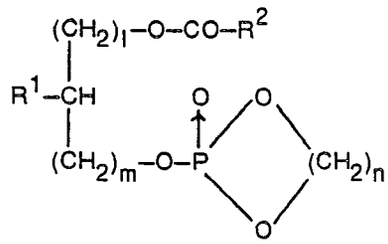


VI

dans laquelle R^1, R^2, *l* et *m* ont les significations indiquées ci-dessus pour la formule I avec de l'oxytrichlorure de phosphore et ensuite on fait réagir avec un alcanediol de formule IX:

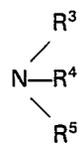
$$HO—(CH_2)_n—OH \qquad IX$$

dans laquelle *n* a la signification donnée ci-dessus dans la formule I avec emploi facultatif des bases auxiliaires et de solvants inertes, pour obtenir les composés cycliques de phosphore de formule X:



X

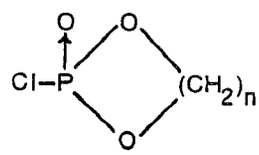
dans laquelle R^1, R^2, *l*, *m* et *n* ont les significations données ci-dessus pour la formule I et on fait ensuite réagir les composés X avec une amine de formule VIII:



VIII

dans laquelle *n* a la signification donnée ci-dessus pour la formule I, dans un solvant organique facultativement sous pression.

7. Procédé de préparation de composés de formule X selon la revendication 6, caractérisé en ce qu'on fait réagir les composés de formule VI selon la revendication 5, avec un composé cyclique de phosphore de formule XI:



XI

dans laquelle *n* a la signification donnée ci-dessous pour la formule I au sein d'un solvant organique inerte avec addition d'une base auxiliaire.