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Glycerol derivatives

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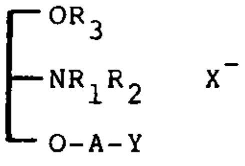
TITLE:

Glycerol Derivatives

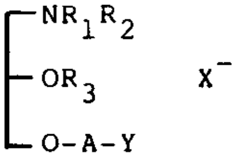
DESCRIPTION:

The invention relates to glycerol derivatives which are of interest for their antitumoral activity, to a method for their preparation and to pharmaceutical compositions containing them.

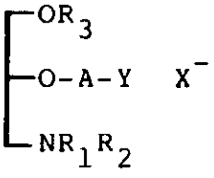
The invention provides glycerol derivatives of the general formula Ia, Ib and Ic



Ia



Ib



Ic

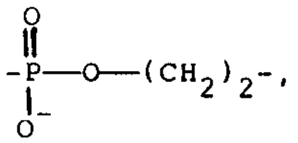
wherein:

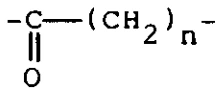
R_1 represents a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms;

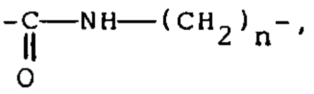
R_2 represents a straight chain or branched chain alkyl group having from 10 to 24 carbon atoms;

R_3 represents an aryl group, an alkyl group having from 1 to 6 carbon atoms, an alkylcarbamoyl group having from 2 to 7 carbon atoms or a dialkylcarbamoyl group in which each alkyl group has from 1 to 6 carbon atoms;

A represents a group of the formula $-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle O^-}{|}}{P}}-O-(CH_2)_2-$, $-\underset{\underset{\displaystyle O}{\|}}{C}-(CH_2)_n-$ or $-\underset{\underset{\displaystyle O}{\|}}{C}-NH-(CH_2)_n-$, n being an integer of from 2 to 10;





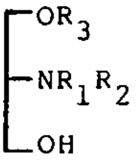


Y represents an ammonium group, an alkyl ammonium group having from 1 to 6 carbon atoms, a dialkylammonium or trialkylammonium group in which each alkyl group independently has from 1 to 6 carbon atoms, or a saturated or unsaturated heterocyclic group containing a quaternary nitrogen hetero atom; and

if A has the first of the values given above X^- has no value but if A has the second or third of the values given above X^- represents a pharmaceutically acceptable anion.

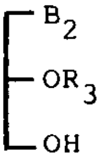
The invention further provides pharmaceutically acceptable salts of the glycerol derivatives Ia, Ib and Ic as above defined.

The invention also provides a process for the preparation of glycerol derivatives Ia, Ib and Ic as above defined, the process comprising reacting a propanol derivative of the general formula



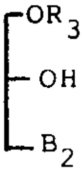
,

IIA



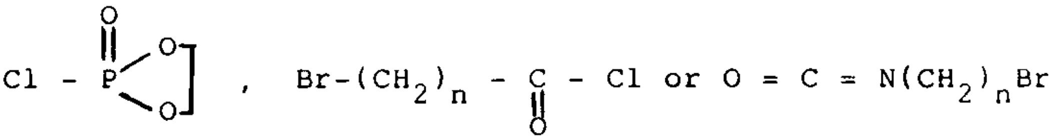
IIb

or



IIc

wherein R_1R_2 and R_3 are as above defined and B_2 represents a group of the formula $-NR_1'R_2$ or $-N(SO_2CH_2\emptyset)R_2$ wherein R_1' represents an alkyl group having from 1 to 5 carbon atoms, R_2 is as above defined and $\emptyset$ represents a phenyl group with an oxo compound which has the formula



$Cl-P(=O)\langle O\text{-}O \rangle$, $Br-(CH_2)_n-\underset{\underset{O}{\|}}{C}-Cl$ or $O=C=N(CH_2)_nBr$

wherein n is as above defined; the said reaction being (a) carried out in the presence of an excess of a nitrogen compound which is ammonia, an alkylamine having from 1 to 6 carbon atoms, a dialkylamine or trialkylamine in which each alkyl group independently has from 1 to 6 carbon atoms or a saturated or unsaturated heterocyclic compound containing a nitrogen hetero atom, or (b) followed by reaction of the product with one of the nitrogen compounds listed in (a); and, if the product obtained by route (a) or route (b) contains a benzylsulphonyl protected nitrogen atom, hydrogenolysing it to form a glycerol derivative I in which R_1 represents a hydrogen atom.

The process according to the invention may be conducted in a single step, option (a) above, or as two steps, option (b) above. In either event, it is preferably carried out under a non-oxidising or inert atmosphere such as nitrogen; and desirably the propanol derivative is reacted with a 10 to 100% stoichiometric excess of the oxo compound.

When carried out as a two step process, the first step, that is the reaction of the propanol derivative II with the oxo derivative, is preferably carried out in an aprotic solvent in the presence of an organic base such as triethylamine. The most suitable temperature is from -10°C to ambient. The second step may then be carried out by heating the product of the first step with the nitrogen compound. Heating is preferably at 50 to 80°C. The product of the first step may simply be suspended or dissolved in the nitrogen compound and heated. When this is impracticable, e.g. because of the low boiling points of ammonia and the mono-, di- and tri-alkylamines of low molecular weight, a solvent may be used and the nitrogen compound is then preferably used in a 30 to 50% stoichiometric excess relative to the product of the first step.

When carried out as a one step process, the reaction is preferably conducted at 50 to 80°C. The nitrogen compound may, as in the second step of the two step process, be used to suspend or dissolve the propanol derivative II and the oxo derivative, either alone or in conjunction with an aprotic solvent.

It should be noted that if the desired glycerol derivative is of the general formula Ib or Ic and R_1 represents a hydrogen atom, it is necessary to protect the secondary amino group with a benzylsulphonyl group. This can be removed at the end of the reation by hydrogenolysis. Such protection is not necessary when preparing compounds of the general formula Ia, since the secondary amino group is then in a sterically hindered position.

Reaction scheme I below illustrates the process according to the invention as it relates to the preparation of the glycerol Ia; the corresponding reaction schemes for the preparation of the glycerol derivatives Ib and Ic are readily deduced by the skilled chemist and therefore need not be shown. In Reaction Scheme I, Z represents a nitrogen compound which is the parent to one of the quaternary nitrogen groups represented by Y.

Glycerol derivatives, and more particularly phosphocholine derivatives, have been described in EP 130527; one of these related compounds, effective in cancer treatment, 3-octadecylamino-1-tetradecyloxy-propan- -2-phosphocoline, and a reference compound, Et-18-OCH_3 (methoxy-PAF; Andreesen; 1988), have been retained for comparison purposes with the compounds of the invention. The results have shown that the compounds of the invention have a higher antitumoral activity, as evidenced in the pharmacological tests herewith.

Lastly, the invention provides a pharmaceutical composition comprising a glycerol derivative according to the invention or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

The starting materials IIa, IIb and IIc may be prepared according to the reaction schemes II, III, IV and V below. In particular:
The starting material II may be prepared according to reaction scheme II: the particularity of these reactions consists in the step 3a — 4a : the mechanism comprises 2 SN_2 substitutions, with migration of the $-OR_3$ and $-NR_1R_2$ groups, as described by K. Suzuki, K. Okano in Synthesis 723 (Sept. 1983).

The starting material IIb may be prepared:

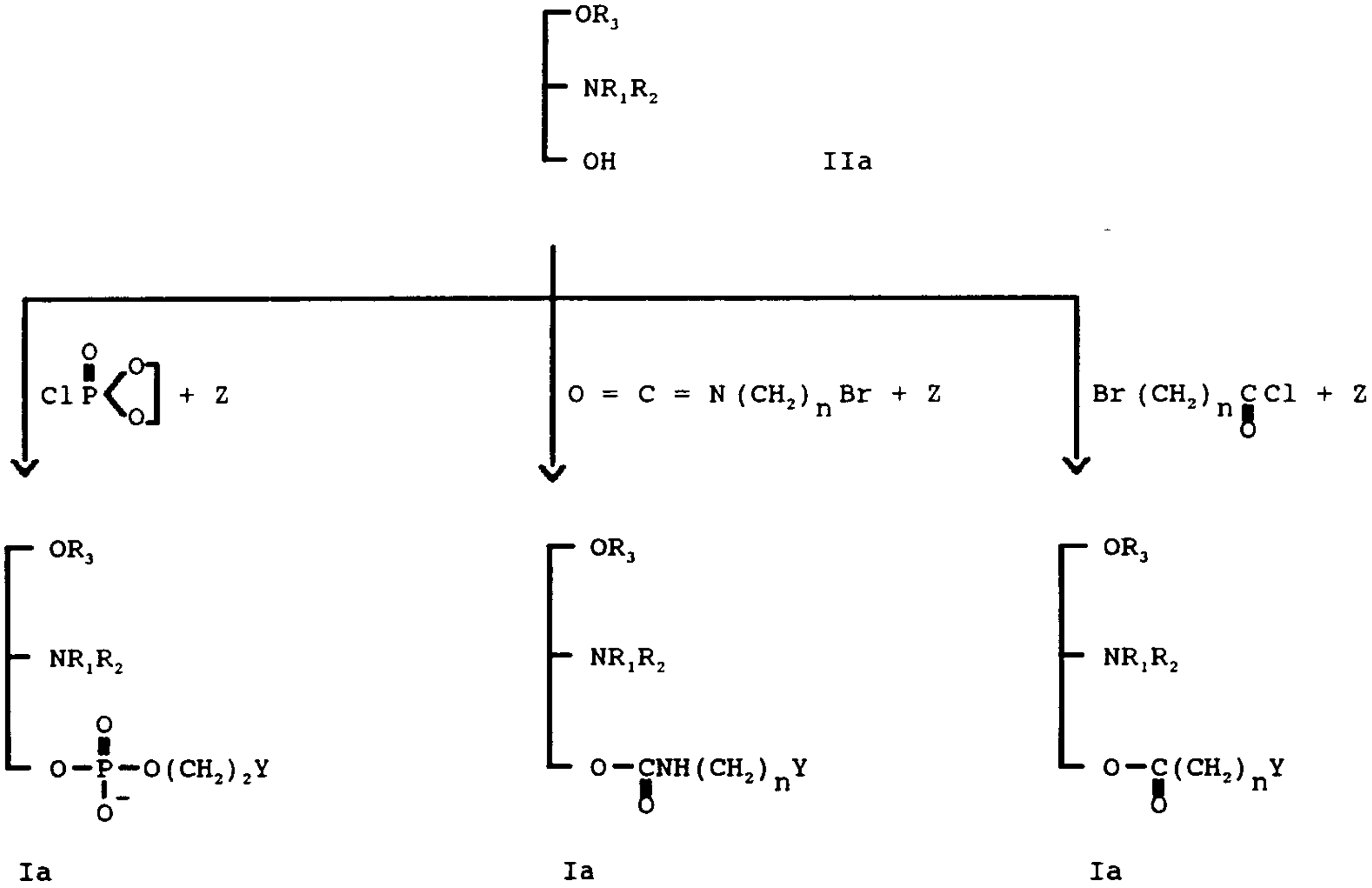
- according reaction scheme III: the compound IIb may comprise a protective group, when the final product Ib is such that R_1 stands for hydrogen. A deprotection by hydrogenolysis will be conducted on the final product;

- according reaction scheme IV, route A or B, specifically when R_3 represents -CONH-alkyl or -CON--dialkyl radical; the starting material 6b of reaction scheme IV is identical with compound 2a of reaction scheme II.

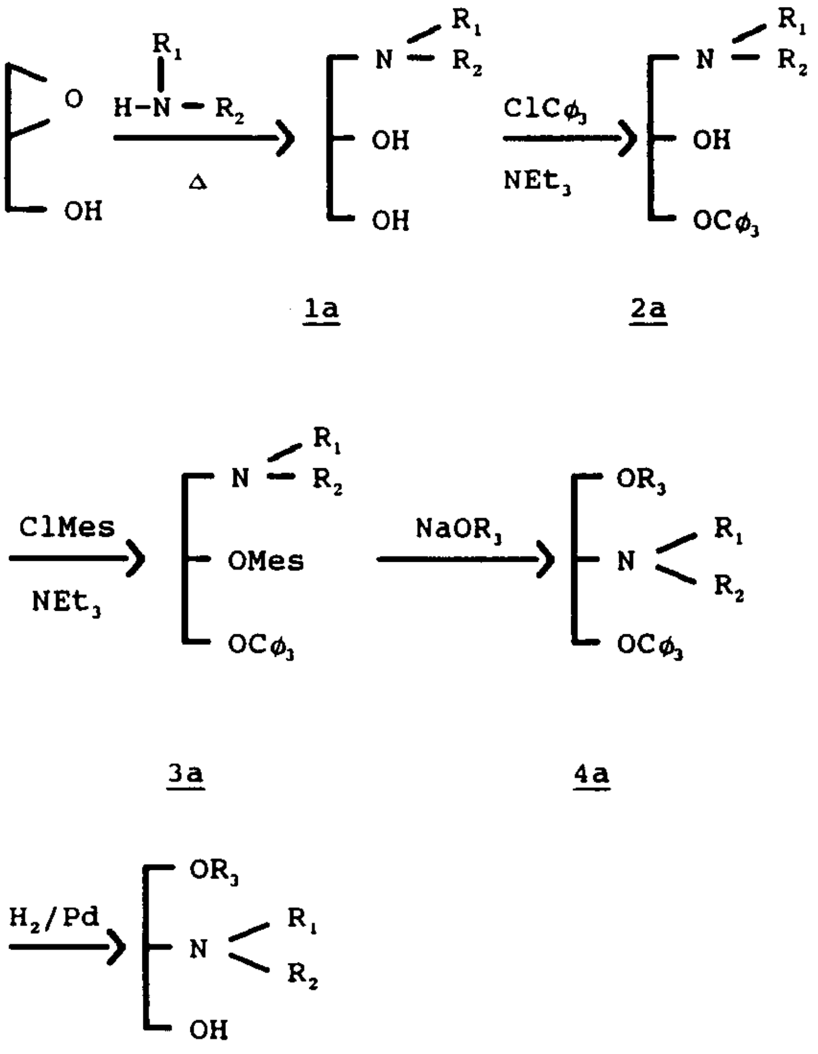
As regards the starting material IIc, reaction scheme V, please refer starting material IIb, first paragraph.

These steps are described below in the preparative examples.

REACTION SCHEME I



Reaction Scheme II

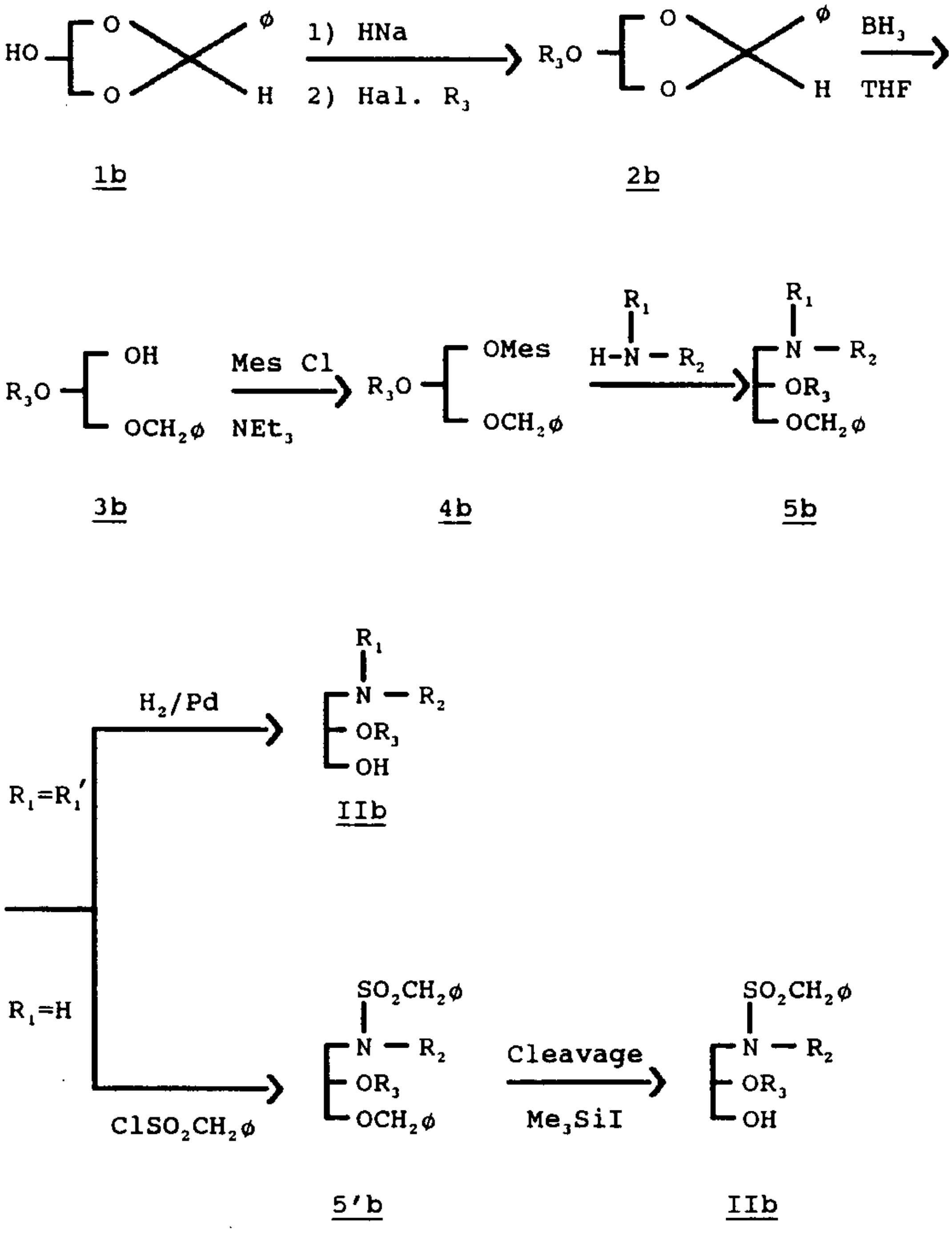


1a 2a

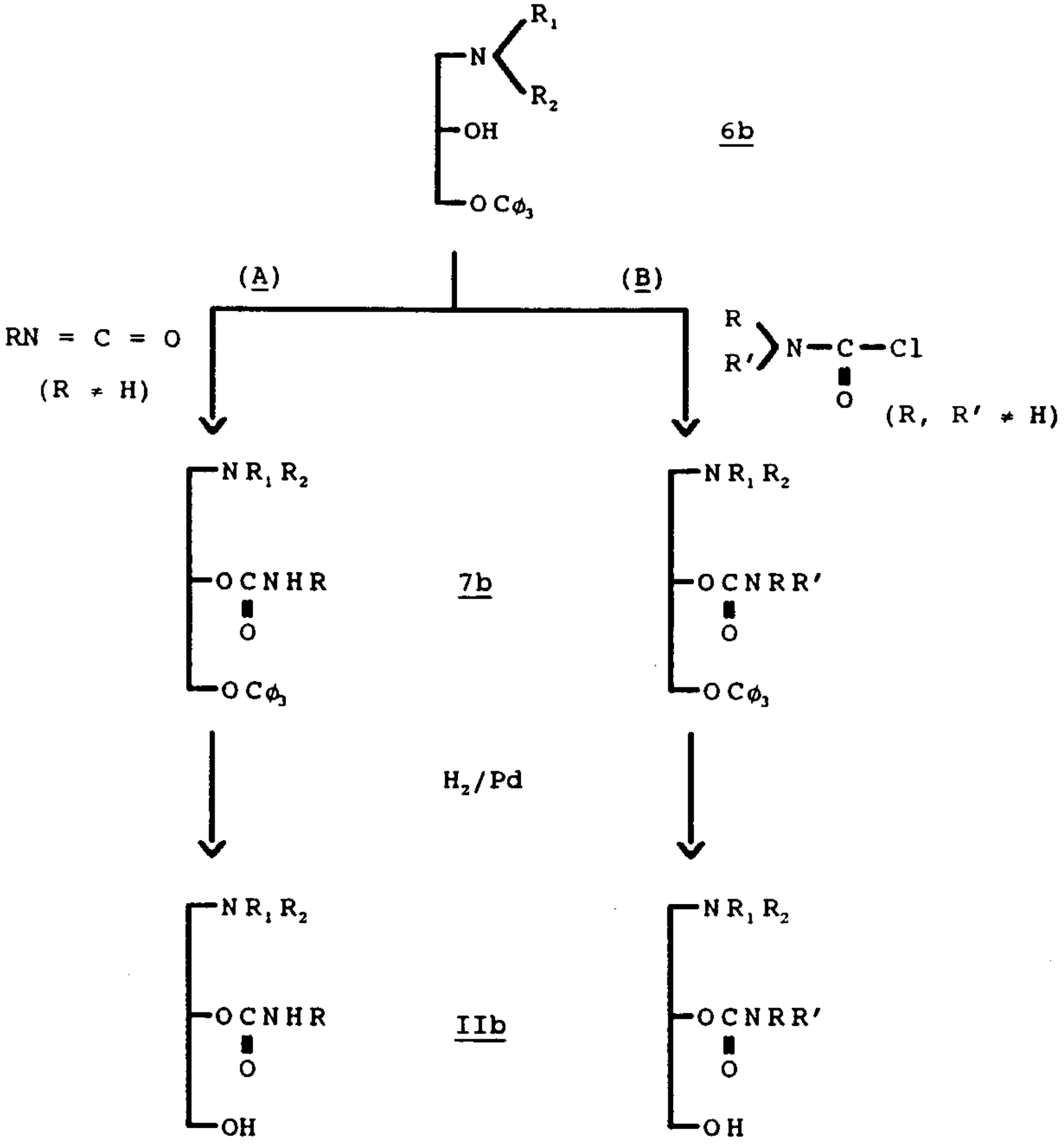
3a 4a

IIa

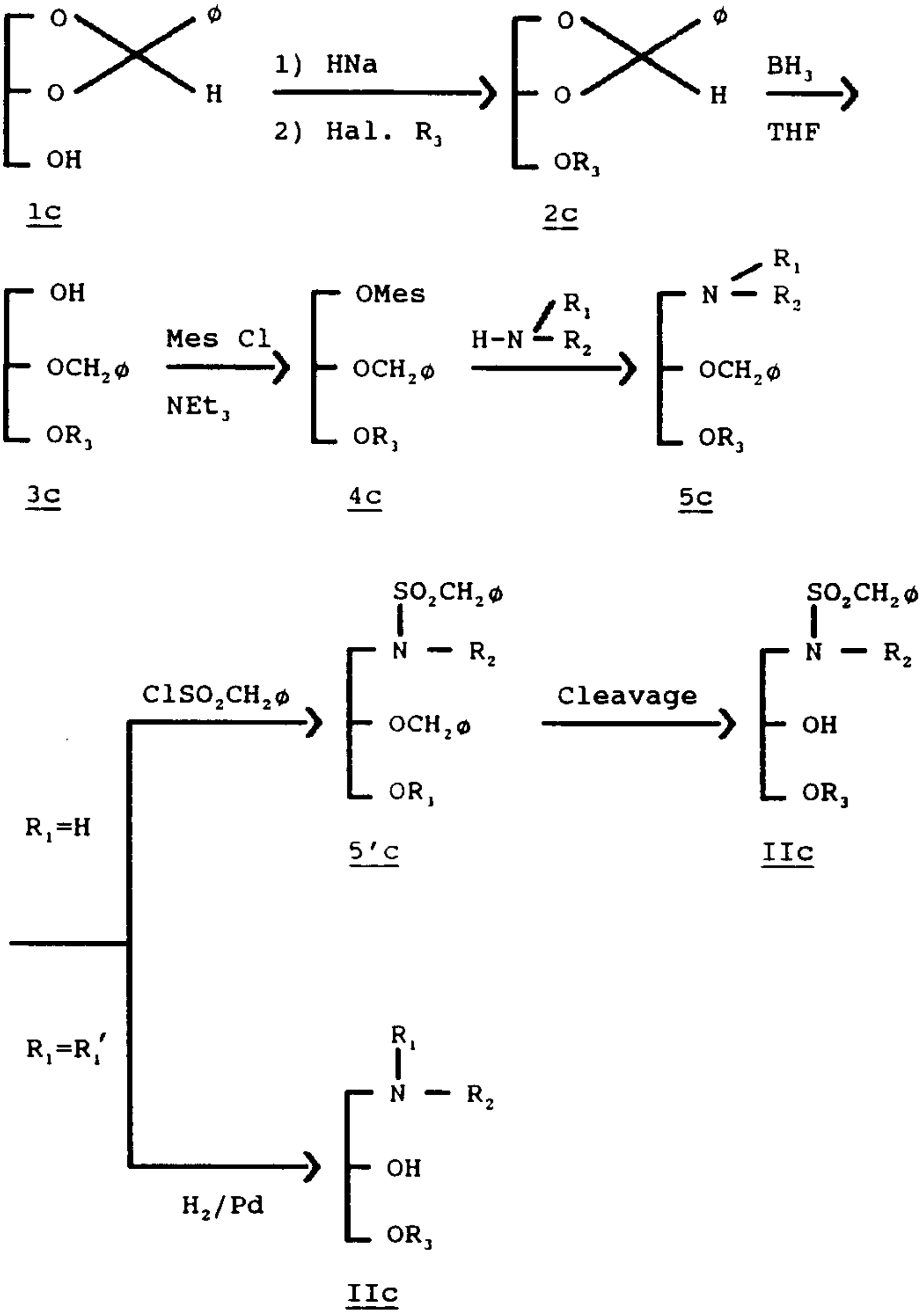
Reaction Scheme III



Reaction Scheme IV



Reaction Scheme V



I. Preparative example of the starting material IIa, according to the reaction scheme II: R_1=CH_3, R_2=$C_{18}H_{37}$, R_3=CH_3

Step 1:
3-(N-methyl-octadecylamino)-1,2-propanediol (1a)

A mixture of glycidol (4 ml, 60 mmol) and N-methyl-octadecylamine (16 g, 60 mmol) in dry toluene (50 ml) was refluxed under stirring for 3 hours. After evaporation of the solvent, the residue was crystallized to yield 16 g (84%) of the title compound. m.p. 59°C (Hexane).

M=357
TLC rf: 0.25 ($CHCl_3$/MeOH, 80:20 v/v)
IR (cm^{-1}) (Nujol ATM) 3300 (OH); 1090,1050 (C-O)
^{1}H-NMR: $CDCl_3$, δ (TMS) 300 MHz
0.82 (t, 3H, CH_3); 1.25 [s, 30H, $(CH_2)_{15}$]; 1.45 (t, 2H, $NCH_2C\underline{H_2}$); 2.3 (s, 3H, NCH_3); 2.5 (m, 4H, CH_2-N-CH_2); 3.3 (large s., 1H, OH); 3.5 (m, 2H, H_2COH); 3.75 (m, 1H, CHOH).

Step 2:
3-(N-methyl-octadecylamino)-1-trityloxy-propan-2-ol (2a)

50 mmol of 1a was treated for 12 hours with 60 mmol of trityl chloride and 120 mmol of triethylamine in 150 ml of boiling toluene. After conventional working up, the remaining oil was chromatographed (Flash chromatography, eluent chloroform) and gave 2a (yield 85%) m.p. 45°C.

TLC rf: 0.44 ($CHCl_3$/MeOH 95:5 v/v)
IR (cm^{-1}) 3500 (OH); 3080, 3050, 3020 (ArCH); 1600 (C=C); 1080 (C-O)
^{1}H-NMR: 300 MHz, $CDCl_3$, δ (TMS)
2.3 (s, 3H, NCH_3); 2.5 (m, 4H, CH_2-N-CH_2); 3.2 (2m, 2H, CH_2Otrityl); 3.9 (m, 1H, $\underline{H}$-COH); 7.3, 7.5 (m, 15H, trityl).

Step 3:

3-(N-methyl-octadecylamino)-2-methanesulphonyloxy-1-trityl-oxy-propane (3a)

18 g (30 mmol) of 2a was dissolved in 100 ml of dry diethyl ether and 50 ml of dichloromethane. 6.84 g (60 mmol) of methanesulphonyl chloride in 50 ml of dichloromethane was added under stirring, and the mixture was refluxed for 5 hours. Water was then added, and the organic phase was decanted, dried and evaporated. The crude product was chromatographed (eluent as in Step 2), yielding 16.7 g of 3a (80%).

M=677

TLC rf: 0.25 ($CHCl_3$)

IR (cm^{-1}) 1600 (C=C); 1370, 1180 (SO_2); 1080 (C-O)

^1H-NMR: 300 MHz $CDCl_3$

2.2 (s, 3H, NCH_3); 2.4 (m, 2H, NCH_2); 2.65 (m, 2H, CH_2N); 3 (s, 3H, CH_3SO_2); 3.35 (m, 2H, CH_2OTr); 4 (m, 1, $CHOSO_2$).

Step 4:

3-methoxy-2-(N-methyl-octadecylamino)-1-trityloxy propane (4a)

This compound was prepared by reacting 3a with sodium methoxide. Yield 68%.

M=613

TLC rf: 0.42 ($CHCl_3$/MeOH); 98:2 ; v/v)

IR (cm^{-1}) 1120 (C-O-Me) 1050 (C-O)

^1H-NMR: 300 MHz $CDCl_3$ δ (TMS)

2.2 (s, 3H, NCH_3); 2.4 (m, 2H, NCH_2); 3.05 (quintet, 1H, CHN); 3.3 (s, 3H, OCH_3); 3.35 (d, 2H, $C\underline{H_2}OCH_3$); 3.6 (d, 2H, CH_2OTr).

Step 5:

3-methoxy-2-(N-methyl-octadecylamino)-propanol (IIa)

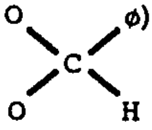
This compound was obtained by hydrogenolysis for 5 hours at 40°C at 40 psi (275880 pascals) of 4a in chloroform, using 10% palladium-on-charcoal as catalyst.

TLC rf: 0.17 ($CHCl_3$/MeOH; 95:5; v/v) M=399.
IR (cm^{-1}) 3410 (OH); 1120 (C-O-Me); 1050 (C-O-C)
^{1}H-NMR: 300 MHz, δ
2.25 (s, 3H, N-CH_3); 2.5 (m, 2H, NCH_2); 3 (m, 1H, $C\underline{H}N$); 3.30 (m, 3H, $C\underline{H}_2OCH_3$, $O\underline{H}$); 3.35 (s, 3H, OCH_3); 3.6 (m, 2H, CH_2OH).

II. Preparative example of the starting material IIb according reaction scheme III: $R_1=CH_3$, $R_2=C_{18}H_{37}$, $R_3=CH_3$

Step 1:
2-phenyl-5-methoxy-1,3-dioxane (2b)
2-phenyl-5-hydroxy-1,3-dioxane 1b was obtained according to Verkaade P.E. and Van Roon J.D. (Rec. Trav. Chim. Pays-Bas, 61, 831, 1942). m.p. 80°C.

10 g of the sodium salt of 1b, obtained by reaction with sodium hydride in dimethylformamide, was treated with 16 g of methyl iodide. The mixture was stirred at 50°C for 5 hours, and the dimethylformamide was eliminated in vacuo. The residue was dissolved in dichloromethane, washed and dried. The solvent was evaporated off and the product was chromatographed on silica gel (eluent : dichloromethane) to give 2b.

Yield: 75%
mp: 51°C; M=194
TLC rf: 0.32 (petroleum ether/diethyl ether 50:50)
IR (cm^{-1}) 3100, 3060, 3040 (CH,ϕ), 1600 (C=Cl), 1100 (C-O)
^{1}H-NMR: 60 MMz, $CDCl_3$ TMS (δ)
3.4(s, 3H, OCH_3); 3.8 (s, 1H, HCOMe); 4 (m, 4H, CH_2-O); 5.5 (s, 1H, ); 7.4 (m, 5H, ϕ).

Step 2 :

3-benzyloxy-2-methoxy-propanol (3b)

4.2 g of 2b was dissolved in 10 ml of tetrahydrofuran at 0°C. A solution of BH_3 in tetrahydrofuran (1M, 30 ml) was added slowly, under stirring. Stirring was continued for 48 hours at room temperature. The mixture was then cooled to 0°C, quenched with cold water and extracted with diethyl ether. The solvent was eliminated and the crude product was chromatographed (eluent petroleum ether/diethyl ether, successively 80:20 and 70:30 by volume), yielding 2.6 g of 3b (62%).

TLC rf: 0.23 (petroleum ether/diethyl ether 50:50 v/v) viscous. M=196
IR (cm^{-1}) 3400 (OH) 3100-3060-3040 (CH,ϕ) 1600 (C=C) 1100 (C-O)
^{1}H-NMR: $CDCl_3$, TMS. (δ) 60 MHz
2.6 (1H, OH); 3.4 (s, 3H, OCH_3); 3.5 (m, 5H, glycerol); 4.5 (s, 2H, $CH_2\,\phi$); 7.3 (5H, ϕ).

Step 3 :

3-benzyloxy-2-methoxy-1-methanesulphonyloxy-propane (4b)

To a solution of 5.88 g (30 mmol) of 3b and 10 ml of triethylamine in 100 ml of dry diethyl ether and 50 ml of dichloromethane, was added under stirring 6.84 g (60 mmol) of methanesulphonyl chloride in 50 ml of dichloromethane, and the mixture was refluxed for 5 hours. Water was then added, and the organic phase was decanted, dried and evaporated. The crude product was chromatographed (eluent petroleum ether/diethyl ether 80:20 by volume), to yield 6 g (74%) of 4b.

TLC rf: 0.35 ($CHCl_3$) viscous. M=274
IR (cm^{-1}) 1600 (C=C); 1350 (SO_2); 1170 (SO_2); 1100 (C-O-)
^{1}H-NMR: $CDCl_3$, TMS (δ) 60 MHz
3 (s, 3H, SO_2CH_3); 3.4 (s, 3H, OMe); 3.5 (d, 2H, $CH_2OCH_2\,\phi$); 3.8 (m, 1H, HCOMe); 4.4 (m, 2H, $C\underline{H}_2OSO_2$); 4.6 (s, 2H, $CH_2\phi$); 7.4 (5H, ϕ).

Step 4:

3-benzyloxy-2-methoxy-N-methyl-N-octadecyl-propylamine (5b)

5.4 g (20 mmol) of 4b was dissolved in 15 ml of dimethylsulphoxide and added to a solution of 5.7 g (20 mmol) of N-methyl-octadecylamine and 1.4 ml of triethylamine in 60 ml of dimethylsulphoxide. The mixture was stirred at 80°C for 24 hours. The dimethylsulphoxide was eliminated. The residue was dissolved in dichloromethane, washed with water and dried. The crude product was chromatographed (eluent dichloromethane : methanol 98:2 by volume), yielding 4.2 g of 5b (46%).

TLC rf: 0.42 (CH_2Cl_2/MeOH 95:5, v/v) viscous. M=461
IR (cm^{-1}) 1100 (C-O-)
^{1}H-NMR: $CDCl_3$, TMS (δ) 60MHz
0.9 (t, 3H, CH_3); 1.25 (large sing, 32H); 2.3 (s, 3H, NCH_3); 2.6 (m, 4H, CH_2-N-CH_2); 3.45 (s, 3H, OCH_3); 3.6 (m, 3H, $C\underline{H}OMe$ and $C\underline{H}_2OCH_2\phi$); 4.6 (s, 2H, $CH_2\ \phi$); 7.4 (5H, ϕ).

Step5 :

3-(N-methyl-octadecylamino)-2-methoxy-propanol (IIb)

This compound was obtained by hydrogenolysis for 5 hours at 40°C at 40 psi(275880 pascals) of 5b in chloroform, using 10% palladium-on-charcoal as catalyst.

TLC rf: 0.35 (CH_2Cl_2/MeOH, 95:5, v/v). M=371
IR (cm^{-1}) 3450 (OH); 1110 (C-O-Me); 1060 (C-OH)
^{1}H-NMR: 60MHz, $CDCl_3$, δ
2.3 (s, 3H, NCH_3); 2.6 (m, 4H, CH_2NCH_2); 3.45 (s, 3H, OCH_3); 3.6 (m, 3H, $C\underline{H}OMe$ and $C\underline{H}_2OH$); 5.3 (1H, OH).

III. Preparative example of the starting material IIb according reaction scheme III: $R_1=CH_3$, $R_2=C_{18}H_{37}$, $R_3=C_2H_5$

The procedure was the same as described in the preparative example II, except that ethyl iodide was used in Step 1 in place of methyl iodide.

Step 1:
2-phenyl-5-ethoxy-1,3-dioxane (2b)
yield: 70%
TLC rf: 0.74 (CH_2Cl_2/MeOH, 98:2, v/v)

Step 2:
3-benzyloxy-2-ethoxy-propanol (3b)
yield: 78%
TLC rf: 0.47 (CH_2Cl_2/MeOH, 98:2, v/v)

Step 3:
3-benzyloxy-2-ethoxy-1-methanesulphonyloxy-propane (4b)
yield: 71%
TLC rf: 0.59 (CH_2Cl_2/MeOH, 99:1, v/v)

Step 4:
3-benzyloxy-2-ethoxy-N-methyl-N-octadecyl-propylamine (5b)
yield: 61%
TLC rf: 0.44 (CH_2Cl_2/MeOH, 95:5, v/v)

Step 5:
3-(N-methyl-octadecylamino)-2-ethoxy-propanol (IIb)
yield: 92%
TLC rf: 0.32 (CH_2Cl_2/MeOH, 95:5, v/v)

IV. Preparative example of the starting material IIb according reaction scheme III: R_1=H, R_2=$C_{18}H_{37}$, R_3=CH_3

The procedure of the steps 1 to 3 is the same as described in the preparative example II, steps 1 to 3.

Step 4 :

3-octadecylamino-2-methoxy-1-benzyloxy-propane (5b)

The procedure is the same as step 4, preparative example II, using octadecylamine instead of N- methyl-octadecylamine.

TLC rf: 0.39 (CH_2Cl_2/MeOH, 95/5, v/v).

Step 5: Protection of the amino-group

3-(N-benzylsulphonyl-octadecylamino)-2-methoxy-1-benzyloxy-propane (5'b)

The compound 5'b was obtained by reaction of benzylsulphonyl chloride on 5b in the presence of NEt_3 with CH_2Cl_2 as solvent, at room temperature for 24 hours.

IR (cm^{-1}) 1350 and 1190 (SO_2)

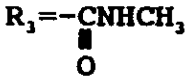
Step 6

3-(N-benzylsulphonyl-octadecylamino)-2-methoxy-propanol (IIb)

The benzyl group was cleaved using Me_3SiI in CH_2Cl_2 at room temperature for 20 minutes.

TLC rf: 0.21 (hexane, ethylacetate 70:30 v/v).

V. Preparative example of the starting material IIb according to reaction scheme IV, route $R_1=CH_3$, $R_2=C_{18}H_{37}$,



$R_3=-\underset{\displaystyle \overset{\|}{O}}{C}NHCH_3$

Step 1:

3-(N-methyl - octadecylamino)-2-methylcarbamoyloxy-1-trityloxy-propane (7b)

The preparation of 3-(N-methyl- octadecylamino)- 1-trityloxy-propan -2-ol 6b is illustrated in the preparative example I, step 2.

A solution of 3-(N-methyl- octadecylamino) -1-trityloxy--propane-2-ol 6b ($6 . 10^{-3}$ M), pyridine (1 ml) and methyl-isocyanate (1.2 ml) in dry benzene (45 ml), was heated at 40°C for three days. After elimination of the solvent, the residue was purified by column chromatography with CH_2Cl_2 as eluent, to give 7b.

Yield: 80% M=661
TLC rf: 0.65 ($CHCl_3$/MeOH, 98:2, v/v)
IR (cm^{-1}) 3350 (NH); 3080, 3050, 3020 (ArCH), 1695 (C=O); 1600 (C=C)
^{1}H-NMR: 60 MHz, $CDCl_3$, TMS, δ
2.8 (d, 3H, $CONHCH_3$); 3.4 (m, 2H, CH_2OTr); 4.8 (m, 1H, $CON\underline{H}CH_3$); 5 (m, 1H, $\underline{H}COCON$)

Step 2:

3-(N-methyl - octadecylamino)-2-methylcarbamoyloxy-propanol (IIb)

This compound was obtained by hydrogenolysis of 7b.

TLC rf: 0.35 ($CHCl_3$/MeOH, 90:10, v/v)
M=414
^{1}H-NMR: 60 MHz, $CDCl_3$, TMS, δ
1.8 (1H, OH); 3.8 (d, 2H, CH_2OH); 5 (m, 1H, $\underline{H}COCON$); 6.4 (1H, $CON\underline{H}CH_3$)

VI. Preparative example of the starting material IIb according to reaction scheme IV, route **B: $R_1=CH_3$, $R_2=C_{18}H_{37}$, $R_3=$**

$R_3=-\underset{\displaystyle \| \atop O}{C}N(CH_3)_2$

Step 1:

3-(N-methyl octadecylamino)- 2-[N,N-(dimethyl)-carbamoyloxy]-1-trityloxy-propane (7b)

A solution of 3-(N-methyl-octadecylamino)- 1-trityloxy-propan -2-ol 6b (5.4 mmol) and 1.4 g (13.5 mmol) of dimethylcarbamoyl chloride in 30 ml of pyridine, was refluxed for three days. After elimination of pyridine, the residue was dissolved in dichloromethane, washed and dried. The solvent was evaporated and the crude product chromatographed on silica gel to yield 1.53 g (42%) of 7b.

M=675

TLC rf: 0.1 (CH_2Cl_2/MeOH, 91:1, v/v)

IR (cm^{-1}) 1700 (C=O); 1600 (C=C)

^{1}H-NMR: 60 MHz, $CDCl_3$, TMS, δ

2.3 (s, 3H, NCH_3); 2.4 (m, 2H, NCH_2); 2.6 (m, 2H, CH_2N); 2.8 [s, 6H, $CON(CH_3)_2$]; 3.3 (m, 2H, CH_2Otrityl); 7.3 (m, 15H, trityl)

Step 2:

3-(N-methyl- octadecylamino)-2-[N,N-(dimethyl)-carbamoyloxy]-propanol (IIb)

The compound IIb was obtained by hydrogenolysis of 7b.

M=428

TLC rf: 0.43 (CH_2Cl_2/MeOH, 90:10, v/v)

IR (cm^{-1}) 1700 (C=O)

^{1}H-NMR: 60 MHz, $CDCl_3$, TMS, δ

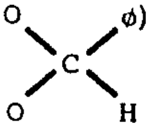
2.9 [s, 6H, $N(CH_3)_2$]; 3.8 (d, 2H, CH_2OH); 4 (1H, OH); 4.9 (m, 1H, HCOCON)

VII. Preparative example of the starting compound IIc, according to the reaction scheme V: $R_1=CH_3$, $R_2=C_{18}H_{37}$, $R_3=CH_3$

Step 1:

2-phenyl-4-methoxymethyl-1,3-dioxolan (2c)

This compound was obtained by the same procedure as described in preparative example II, step 1 but starting from 2-phenyl-4-hydroxymethyl-1,3-dioxolan 1c instead of 2-phenyl-5-hydroxy-1,3-dioxane 1b. Yield 75%. Viscous product.

TLC rf: 0.60 (CH_2Cl_2/MeOH, 98:2 v/v)
^{1}H-NMR: $CDCl_3$, TMS, 60MHz
δ: 3.35 (s, 3H, OCH_3); 3.6 (m, 2H, CH_2OCH_3); 3.9 (m, 3H, CH_2O, CHO); 5.8 (d, 1H, 

); 7.4 (m, 5H, ϕ).

Step 2:

3-methoxy-2-benzyloxy-propanol (3c)

This compound was obtained by the same procedure as described in preparative example II, step 2, but starting from 2-phenyl-4-methoxymethyl-1,3-dioxolan 2c instead of 2-phenyl-5-methoxy-1,3-dioxane 2b.

Yield: 71%
TLC rf: 0.23 (petroleum ether/diethylether, 50:50 v/v)
^{1}H-NMR: $CDCl_3$, TMS, 60MHz, δ
2.5 (1H, OH); 3.3 (s, 3H, OCH_3); 3.6 (m, 5H, glycerol backbone); 4.6 (s, 2H, $CH_2\phi$); 7.3 (5H, ϕ).

Step 3:

3-methoxy-2-benzyloxy-1-methanesulphonyloxy-propane (4c)

This compound was obtained by the same procedure as described in preparative example II, step 3, but starting from 3-methoxy-2-benzyloxy-propanol 3c instead of 3-benzyloxy-2-methoxy-propanol 3b.

Yield: 64%

TLC rf: 0.35 ($CHCl_3$)
^{1}H-NMR: $CDCl_3$, TMS, 60MHz, δ
3 (s, 3H, SO_2CH_3); 3.4 (s, 3H, OCH_3); 3.5 (d, 2H, $C\underline{H}_2OCH_3$); 3.8 (m, H, HC-OCH_2ø); 4.4 (m, 2H, CH_2OSO_2); 4.65 (s, 2H, CH_2ø); 7.3 (5H, ø).

Step 4:
3-methoxy-2-benzyloxy-N-methyl-N-octadecyl-propylamine (5c)
This compound was obtained by the same procedure as described in preparative example II, step4 , but starting from 3-methoxy-2-benzyloxy-1-methanesulphonyloxy-propane 4c instead of 3-benzyloxy-2-methoxy-1-methanesulphonyloxy-propane 4b.

Yield: 50%
TLC rf: 0.42 (CH_2Cl_2/MeOH, 95:5, v/v)
^{1}H-NMR: 60MHz, δ
0.9 (t, 3H, CH_3); 1.3 (large s, 32H); 2.3 (s, 3H, NCH_3); 2.5 (m, 4H, CH_2NCH_2); 3.4 (s, 3H, OCH_3); 3.6 (m, 3H, $C\underline{H}_2OMe$, $C\underline{H}OCH_2$ø); 4.7 (s, 2H, CH_2ø); 7.3 (5H, ø).

Step 5:
3-(N-methyl-octadecylamino)-1-methoxy-propan-2-ol (IIc)
This compound was obtained by hydrogenolysis of 5c under the conditions described in preparative example II, step 6 .

Yield: 90%
TLC rf: 0.35 (CH_2Cl_2/MeOH, 95:5, v/v)

VIII. Preparative example of the starting compound IIc, according to the reaction scheme V: R_1=H, R_2=$C_{18}H_{37}$, R_3=CH_3

The steps 1 to 3 are the same as described in preparative example VII, steps 1 to 3.

Steps 4 to 6:

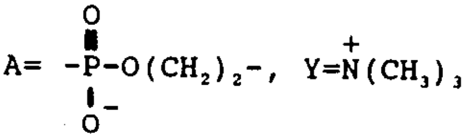
The procedure of preparation of 3-methoxy-2-benzyloxy-N-octadecyl-propylamine (5c), of the protection reaction of the amino group to obtain 3-methoxy-2-benzyloxy-N-(benzyl-sulphonyl-octadecyl)-propylamine (5'c) and of the cleavage of the benzyl group, was the same as described in preparative example IV, steps 4 to 6.

The invention will be better understood from the description of the following examples.

Example 1:

3-methoxy-2-(N-methyl-octadecylamino)-propanol phosphocholine

Compound of the formula Ia wherein $R_1=CH_3$, $R_2=C_{18}H_{37}$, $R_3=CH_3$,



$$A= -\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}-O(CH_2)_2-,\quad Y=\overset{+}{N}(CH_3)_3$$

2 g (5 mmol) of 3-methoxy-2-(N-methyl-octadecylamino)-propanol (IIa) and 3 ml of triethylamine were dissolved in 20 ml of dry benzene, and the mixture was cooled to 5°C under nitrogen circulation. 1 g (7 mmol) of 2-chloro-2-oxo-1,3,2-dioxaphospholane in 4 ml of benzene was added under stirring, and stirring was continued overnight. The amino salt was filtered off and washed with benzene. The filtrate was evaporated to dryness under reduced pressure. The residue was dissolved in 20 ml of dry methyl cyanide and transferred to a reactor. 20 ml of methyl cyanide, saturated with gaseous trimethylamine was added, and the mixture was heated at 65°C for 24 hours. A solid separated on cooling. It was filtered off and chromatographed on silica gel (eluent chloroform : methanol 90:10, then 70:30 by volume, then methanol) to yield 1.1 g (39%) of the title compound.

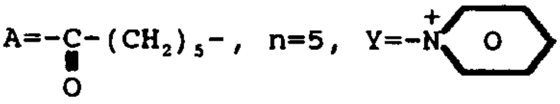
M=564 m.p. 244°C.
TLC rf: 0.256 ($CHCl_3/MeOH/NH_4OH$; 70:30:7, v/v/v)
IR (cm^{-1}) 1240 (P=O); 1090 (C-O); 1040 (P-O-)
^1H-NMR: 500 MHz CD_3OD (TMS) δ

0.8 (t, 3H, CH_3); 1.25 [large s, 30H, $(CH_2)_{15}$]; 1.45 (t, 2H, $NCH_2C\underline{H}_2$); 2.3 (s, 3H, NCH_3); 2.45 (m, 2H, NCH_2); 2.9 (m, 1H, CH_2N); 3.3 (s, 3H, OCH_3); 3.35 [s, 9H, $\overset{+}{N}(CH_3)_3$]; 3.5 (m, 2H, $C\underline{H}_2OCH_3$); 3.7 (m, 2H, $CH_2\overset{+}{N}$); 3.95 (m, 2H, CH_2OP); 4.25 (m, 2H, $POCH_2$).

Example 2:

3-methoxy -2-(N-methyl-octadecylamino)-1-[6'-(N-pyridinium)-hexanoyloxy]-propane bromide

Compound of the formula Ia wherein $R_1=CH_3$, $R_2=C_{18}H_{37}$, $R_3=CH_3$,



$A=-\underset{\underset{O}{\|}}{C}-(CH_2)_5-$, n=5, $Y=-\overset{+}{N}$

3-methoxy-2-(N-methyl-octadecylamino)-propanol (IIa) (3.5 g, 9 mmol) and Et_3N (25 mmol) in 15 ml of ethanol free chloroform, were added dropwise to a solution of 5-bromohexanoyl chloride (10 mmol) in 10 ml of the same solvent, at 0°C under nitrogen circulation. The mixture was stirred for 15 hours at room temperature. After evaporation of solvent, 30 ml of dry pyridine was added to the obtained residue, and the mixture was then stirred at 80°C under N_2 for 24 hours. Pyridine was eliminated in vacuo and the residue was purified by column chromatography (eluent $CHCl_3$ then $CHCl_3/MeOH$ 90:10) to yield 2.47 g (70%) of the title compound.

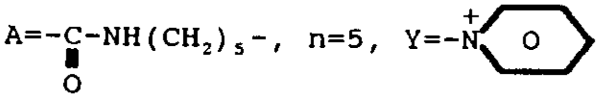
M=627
TLC rf 0.19 ($CHCl_3/MeOH$, 70:30, v/v)
IR (cm^{-1}) 1740 (C=O); 1640 (pyridine)
^1H-NMR: 500 MHz, $CDCl_3$, TMS δ

1.4 (m, 2H, $COCH_2CH_2C\underline{H}_2$); 1.6 (m, 2H, $COCH_2C\underline{H}_2$); 2.1 (m, 2H, $C\underline{H}_2CH_2-\overset{+}{N}$); 2.35 (t, 2H, $COCH_2$); 5.05 (t, 2H, $CH_2\overset{+}{N}$); pyridinium 8.1 (t, 2H, H_β); 8.6 (d, 1H, H_γ); 9.5 (d, 2H, H_α).

Example 3:

3-methoxy - 2-(N-methyl-octadecylamino)-1-[5'-(N-pyridinium)-pentylcarbamoyloxy]-propane bromide

Compound of the formula Ia wherein $R_1=CH_3$, $R_2=C_{18}H_{37}$, $R_3=CH_3$,



$A=-\underset{\underset{O}{\|}}{C}-NH(CH_2)_5-$, $n=5$, $Y=-\overset{+}{N}$

A mixture of 3-methoxy-2-(N-methyl-octadecylamino)-propanol (IIa) (3.5 g, 9 mmol), 5-bromopentylisocyanate (12 mmol) and 30 ml of pyridine, was heated for two days at 80°C under nitrogen circulation. Pyridine was eliminated in vacuo and the obtained residue was dissolved in $CHCl_3$, washed and dried. The solvent was evaporated and the residue was chromatographed (eluent $CHCl_3$ then $CHCl_3$/MeOH, 95:5, 90:10) to yield 2.1 g (40%) of the title compound.

M=642

TLC rf: 0.23 ($CHCl_3$/MeOH, 70:30, v/v)

IR (cm^{-1}) 3350 (NH), 1720, CONH), 1640 (pyridine)

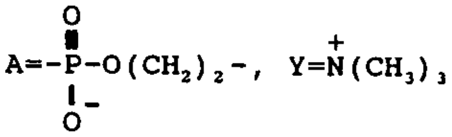
^1H-NMR: 500 MHz, $CDCl_3$, TMS δ

1.4 (m, 2H, $COCH_2CH_2C\underline{H}_2$); 1.6 (m, 2H, $COCH_2C\underline{H}_2$); 2.1 (m, 2H, $C\underline{H}_2-CH_2-\overset{+}{N}$); 3.25 (t, 2H, $CONHCH_2$); 5.05 (t, 2H, $CH_2\overset{+}{N}$); 5.6 (NH); pyridinium 8.1 (t, 2H, H_β); 8.6 (d, 1H, H_γ); 9.5 (d, 2H, H_α).

Example 4:

3-(N-methyl-octadecylamino)-2-methoxy-propanol phosphocholine

Compound of the formula Ib wherein $R_1=CH_3$, $R_2=C_{18}H_{37}$, $R_3=CH_3$



$$A = -\underset{O^-}{\overset{O}{\overset{\|}{\underset{|}{P}}}}-O(CH_2)_2-,\quad Y = \overset{+}{N}(CH_3)_3$$

This compound was prepared by the same method as described in example 1, but starting with 3-(N-methyl-octadecylamino)-2-methoxy-propanol(<u>IIb</u>), instead of 3-methoxy-2-(N-methyl-octadecylamino)-propanol (<u>IIa</u>).

Yield: 46% M=564

TLC rf: 0.22 ($CHCl_3$/MeOH/NH_4OH, 70:30 7,v/v/v)

IR (cm^{-1}) 1240 (P=O); 1100 (C-O-); 1040 (P-O).

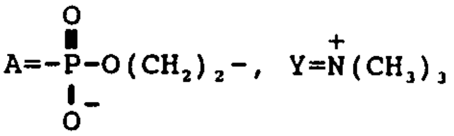
^1H-NMR: 500 MHz, CD_3OD, TMS (δ)

0.9 (t, 3H, CH_3); 1.25 [large s, 30H, $(CH_2)_{15}$]; 1.5 (m, 2H, $NCH_2C\underline{H_2}$); 2.27 (s, 3H, NCH_3); 2.4 (m, 2H, $NC\underline{H_2}$); 2.55 (m, 2H, CH_2N); 3.2 [s, 9H, $\overset{+}{N}(CH_3)_3$]; 3.45 (s, 3H, OCH_3); 3.55 (m, 1H, $C\underline{H}OCH_3$); 3.65 (t, 2H, $CH_2\overset{+}{N}$); 3.9 (m, 2H, CH_2OP); 4.3 (m, 2H, $POCH_2$).

<u>Example 5:</u>

<u>3-(N-methyl-octadecylamino)-2-ethoxy-propanol phosphocholine</u>

Compound of the formula Ib wherein $R_1=CH_3$, $R_2=C_{18}H_{37}$, $R_3=C_2H_5$,



$$A = -\underset{O^-}{\overset{O}{\overset{\|}{\underset{|}{P}}}}-O(CH_2)_2-,\quad Y = \overset{+}{N}(CH_3)_3$$

This compound was prepared by the same procedure as described in example 1, but starting with 3-(N-methyl-octadecylamino)-2-ethoxy-propanol <u>IIb</u> instead of 3-methoxy-2-(N-methyl-octadecylamino) propanol <u>IIa</u>.

Yield: 32% MH^+=579

TLC rf: 0.195 ($CHCl_3$/MeOH/NH_4OH, 70:30:7, v/v/v)

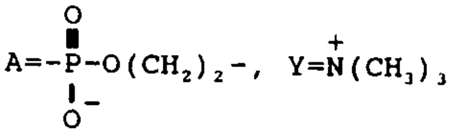
^1H-NMR: 500 MHz, CD_3OD, TMS, δ

0.9 (2t, 6H, $2CH_3$); 1.25 [large s, 30H, $(CH_2)_{15}$]; 1.5 (m, 2H, $NCH_2C\underline{H}_2$); 2.27 (s, 3H, NCH_3); 2.4 (m, 2H, $NC\underline{H}_2$); 2.55 (m, 2H, CH_2N); 3.2 [s, 9H, $\overset{+}{N}(CH_3)_3$]; 3.55 (m, 1H, $C\underline{H}OCH_3$); 3.65 (t+q, 4H, $CH_2\overset{+}{N}+OCH_2$); 3.9 (m, 2H, CH_2OP); 4.3 (m, 2H, $POCH_2$).

Example 6:

3-octadecylamino-2-methoxy-propanol phosphocholine

Compound of the formula Ib wherein R_1=H, R_2=$C_{18}H_{37}$, R_3=CH_3,



$$A = -\overset{\overset{\large O}{\|}}{\underset{\underset{\large O^-}{|}}{P}}-O(CH_2)_2-, \quad Y = \overset{+}{N}(CH_3)_3$$

3-(N-benzylsulphonyl-octadecylamino)-2-methoxy-propanol phosphocholine

This compound was obtained by the same procedure as described in example 1, but starting with 3-N,N-(benzylsulphonyl-octadecylamino-2-methoxy-propanol (IIb) instead of 3-methoxy-2-(N-methyl-octadecylamino)-propanol (IIa).

Yield: 35%

TLC rf: 0.29 ($CHCl_3/MeOH/NH_4OH$, 70:30:7, v/v/v)

^1HNMR: 500 MHz, CD_3OD, TMS (δ)

3.15 [s+m, 12H, $\overset{+}{N}(CH_3)_3$ and $N\langle^{SO_2}_{CH_2}$]; 3.35 (s+m, 5H, OCH_3 and CH_2N-SO_2); 3.55 (m, 3H, $C\underline{H}OCH_3$ and $CH_2\overset{+}{N}$); 4.3 (m, 2H, $POCH_2$); 4.4 (m, 4H, CH_2OP and $SO_2C\underline{H}_2\phi$); 7.40 (5H, ϕ).

3-octadecylamino-2-methoxy-propanol phosphocholine

Deprotection reaction:

This compound was obtained by hydrogenolysis of 3-(N-benzylsulphonyl-octadecylamino)-2-methoxy-propanol phosphocholine, using Raney-Nickel as catalyst.

TLC rf: 0.17 ($CHCl_3/MeOH/NH_4OH$, 70:30:7, v/v/v)

M=550

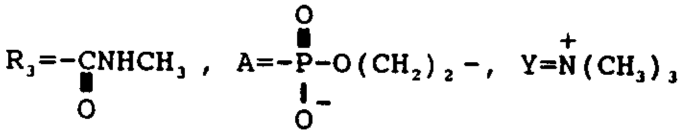
^{1}H-NMR: 500 MHz, CD_3OD, TMS (δ)

3 (m, 2H, NCH_2); 3.15 (m, 3H, NH and CH_2N); 3.45 [s, 9H, $\overset{+}{N}(CH_3)_3$]; 3.65 (s, 3H, OCH_3); 3.8 (m, 3H, $C\underline{H}OCH_3$ and $CH_2\overset{+}{N}$); 4.2 (m, 2H, $POCH_2$); 4.4 (m, 2H, CH_2OP).

Example 7:

3-(N-methyl-octadecylamino)-2-methylcarbamoyloxy-propanol phosphocholine

Compound of the formula Ib wherein $R_1=CH_3$, $R_2=C_{18}H_{37}$,



$$R_3=-\underset{\underset{O}{\|}}{C}NHCH_3\ ,\quad A=-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}-O(CH_2)_2-,\quad Y=\overset{+}{N}(CH_3)_3$$

To a cooled (5°C), stirred solution of 3-(N-methyl-octadecylamino)-2-methylcarbamoyloxy-propanol (<u>IIb</u>) (2.9 g, 7 mmol) and 3 ml of NEt_3 in dry benzene (20 ml), was added 2-chloro-2-oxo-1,3,2-dioxaphospholane (2 g, 14 mmol) in benzene (4 ml) under nitrogen circulation. The mixture was stirred at room temperature for 8 hours, then filtered. The filtrate was evaporated off under reduced pressure. The residue was dissolved in dry CH_3CN (50 ml) and transferred in a reactor. 30 ml of CH_3CN saturated by gazeous NMe_3 were added and the mixture was heated at 65°C for 24 hours. The solvent was evaporated and the residue was chromatographed on silica gel (eluent $CHCl_3$/MeOH, 90:10 then 70:30 and 30:70, then methanol) to yield 1.74 g (43%) of the title compound.

MH^+=581

TLC rf: 0.26 ($CHCl_3$/MeOH/NH_4OH, 70:30:7)

IR (cm^{-1}) 3350 (NH); 1700 (C=O); 1250 (P=O); 1100, 1050 (C-O-C and P-O-C)

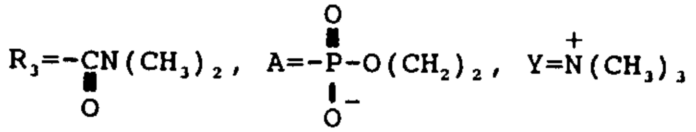
^{1}H-NMR: CD_3OD, δ (TMS), 500 MHz

2.3 (s, 3H, NCH_3); 2.45 (m, 3H, NCH_2); 2.6 (m, 2H, CH_2N); 2.75 (d, 3H, $CONHCH_3$); 3.4 [s, 9H, $\overset{+}{N}(CH_3)_3$]; 3.7 (m, 2H, $CH_2\overset{+}{N}$); 3.95 (m, 2H, CH_2OP); 4.3 (m, 2H, $POCH_2$); 5 (m, 1H, HCOCON); 7 (1H, CONH)

Example 8:

3-(N-methyl- octadecylamino)-2-(N,N- dimethyl-carbamoyloxy)-propanol phosphocholine

Compound of the formula Ib wherein $R_1=CH_3$, $R_2=C_{18}H_{37}$,



$$R_3=-\underset{\underset{O}{\|}}{C}N(CH_3)_2,\quad A=-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}-O(CH_2)_2,\quad Y=\overset{+}{N}(CH_3)_3$$

This compound was prepared by the same procedure as described in example 7 but starting with 3-(N-methyl octadecylamino) - 2-(N,N- dimethyl-carbamoyloxy) - propanol instead of 3-(N-methyl octadecylamino)-2-methylcarbamoyloxy-propanol.

Yield: 40% $MH^+=594$

TLC rf: 0.3 ($CHCl_3/MeOH/NH_4OH$, 70:30:7, v/v/v)

IR (cm^{-1}) 1700 (C=O); 1250 (P=O); 1100,1050 (C-O-C, P-O-C)

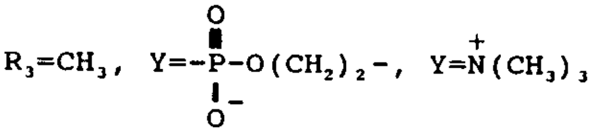
^1H-NMR: CD_3OD, TMS, 500 MHz, δ

2.2 (s, 3H, NCH_3); 2.35 (m, 2H, NCH_2); 2.55 (m, 2H, CH_2N); 2.85 [d, 6H, $CON(CH_3)_2$]; 3.25 [s, 9H, $\overset{+}{N}(CH_3)_3$]; 3.55 (m, 2H, $CH_2\overset{+}{N}$); 3.9 (m, 2H, CH_2OP); 4.25 (m, 2H, $POCH_2$); 4.95 (m, 1H, HCOCON)

Example 9:

3-(N-methyl-octadecylamino)-1-methoxy-propan-2-ol phosphocholine

Compound of the formula Ic wherein $R_1=CH_3$, $R_2=C_{18}H_{37}$,



$$R_3=CH_3,\quad Y=-\overset{\overset{O}{\|}}{\underset{\underset{O^-}{|}}{P}}-O(CH_2)_2-,\quad Y=\overset{+}{N}(CH_3)_3$$

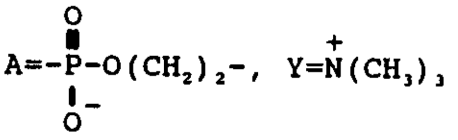
This compound was obtained by the procedure described in example 1 but starting from 3-(N-methyl-octadecylamino)-1-methoxy-propan-2-ol (IIc) instead of 2-(N-methyl-octadecylamino)-3-methoxy-propanol (IIa).

TLC rf: 0.24 ($CHCl_3/MeOH/NH_4OH$, 70:30:7, v/v/v)
Yield: 35%
mp: 248°C
IR (cm^{-1}) 1240 (P=O); 1100 (C-O); 1040 (P-O)
^1H-NMR: 500MHz, CD_3OD, (TMS) δ
0.82 (t,3H,CH_3); 1.25 [s,30H,$(CH_2)_{15}$]; 1.45 (t,2H,N-$CH_2C\underline{H}_2$); 2.2 (s,3H,NCH_3); 2.35 (m,2H,NCH_2); 2.55 (m,2H,CH_2N); 3.2 [s,9H,$\overset{+}{N}2(CH_3)_3$]; 3.35 (s,3H,OCH_3); 3.5 (m,2H,$C\underline{H}_2OCH_3$); 3.6 (m,2H,CH_2N+); 4.25 (m,2H,$POCH_2$); 4.3 (1H,CHOP).

Example 10:

1-octadecylamino-3-methoxy-propan-2-ol phosphocholine

Compound of the formula Ic wherein R_1=H, R_2=$C_{18}H_{37}$, R_3=CH_3,



$$A=-\overset{\displaystyle O}{\underset{\displaystyle O^-}{\overset{\|}{\underset{|}{P}}}}-O(CH_2)_2-,\quad Y=\overset{+}{N}(CH_3)_3$$

This compound was obtained by the procedure as described in example 6, comprising the preparation and the deprotection of 1-(N-(benzylsulphonyl-octadecylamino)-3-methoxy-propan-2-ol phosphocholine.

M=550
TLC rf: 0.20 ($CHCl_3/MeOH/NH_4OH$, 70:30:7, v/v/v)
^1H-NMR: 500 MHz, CD_3OD, (TMS) δ
2.9 (m, 3H, NH and NCH_2); 3.1 (m, 2H, CH_2N); 3.4 [s, 9H, $\overset{+}{N}(CH_3)_3$]; 3.55 (s, 3H, OCH_3); 3.7 (m, 2H, $CH_2\overset{+}{N}$); 3.85 (m, 2H, CH_2OMe); 4.5 (m, 2H, $POCH_2$); 4.6 (m, 1H, CHOP).

TOXICITY

The toxicity of the compounds of the invention, has been determined per os on mice, by usual methods. Their LD_{50} values are higher than 650 mg/kg.

PHARMACOLOGY

The compounds of the invention have been examined for their ability to inhibit in vitro tumor cell proliferation.

They inhibit HL60 and A.427 tumor cell proliferation after 24 hours.
HL60: promyelocytic leukemia cell line
A.427: lung carcinoma cell line
They show a cytostatic effect at the dose of 0.02 mM which is not a toxic dose for the two human tumor cell lines. Overall, the lung carcinoma cell line resulted more sensitive than the promyelocytic leukemia cell line.

The effect of the compounds of the invention on long-term proliferation, has been more precisely described above.

All of the examples of the invention have been tested and compared with two related compounds of the prior art:

- the 1-0-octadecyl- 2-0-methylglycero- 3-phosphocholine (Et-18-OCH_3 or methoxy PAF ; Andreesen, 1988),
- the 3-octadecyl-1-0-tetradecyl-propan-1,2-diol-2-0-phosphocholine [compound (D)].

For this study, a colon adenocarcinoma cell line, called HT.29, have been used; they are anchorage-dependent cells.

The HT.29 cells were grown in Mc Coy medium (Flow Labs), supplemented with 10% foetal bovine serum (FBS; Gibco). The growth media contain 100 U/ml of penicillin and 100 µg/ml of streptomycin (Flow Labs).

The compounds of the invention and the compounds (D) and Et-18-OCH_3, were dissolved in a solution containing 60% ethanol and 40% phosphate buffer saline (PBS; Flow Labs).

Serial dilutions were prepared in PBS. The dose tested was 0.02 mM. The treatment time lasted 24 hours at 37°C.

The effect of the compounds of the invention on long-term cell proliferation and survival, has been evaluated by studying the plating efficiency and colony morphology of HT.29. To carry out this study, 5.10^2 HT.29 cells, previously treated with the different compounds of the invention for 24 hours, were seeded into 25 cm^2 growth area tissue culture flasks.

These cell cultures were then incubated at 37°C for 15 days. At the end of this incubation time, the cell cultures were rinsed twice with PBS, fixed with 70% ethanol for 30 minutes and stained for the same length of time with 10% Giemsa (Sigma Chemicals).

The results are expressed as 'relative plating efficiency (P.E.)' values calculated as follows:

$$P.E. = \frac{\text{Number of colonies formed}}{\text{Number of cells plated}} \times 100$$

and summarized in the following tables.

It has been found that the colonies formed after treatment of compounds of the invention, have lost their regular profile, have a lower reactivity to the Giemsa stain and, overall their size is smaller than that of the untreated colonies.

COMPOUNDS	P.E. (%)
Control	100 ± 4.3
Et-18-OCH3	39 ± 1.5
(D)	34 ± 2.3 **
EX 1	21.9 ± 1.0 ***
EX 2	24.3 ± 1.4 **
EX 3	27.1 ± 2.1 *
EX 4	45.6 ± 3.0 NS

COMPOUNDS	P.E. (%)
EX 5	20.6 ± 1.7 **
EX 6	26.4 ± 1.7 **
EX 7	22.3 ± 2.2 ***
EX 8	19.9 ± 0.9 ***
EX 9	20.2 ± 1.2 **
EX 10	25.4 ± 2.7 *

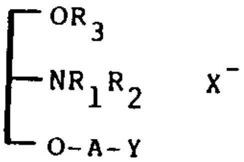
The statistical symbols refer to the comparison between each compound with the reference Et-18-OCH_3. The different symbols: NS, *, ** and *** mean that the result is respectively not significative, significative, very significative and highly significative.

POSOLOGY

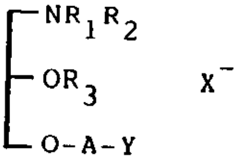
In human therapy, the compounds of the invention are preferably administered by the IV route. Usual posology is from 2.5 to 5 mg/dm^2 of the tumour under treatment per diem, three to six days per month in slow perfusion.

CLAIMS:

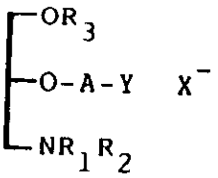
1. A glycerol derivative of the general formula Ia, Ib or Ic



Ia



Ib



Ic

wherein:

R_1 represents a hydrogen atom or an alkyl group having from 1 to 5 carbon atoms;

R_2 represents a straight chain or branched chain alkyl group having from 10 to 24 carbon atoms;

R_3 represents an aryl group, an alkyl group having from 1 to 6 carbon atoms, an alkylcarbamoyl group having from 2 to 7 carbon atoms or a dialkylcarbamoyl group in which each alkyl group has from 1 to 6 carbon atoms;

A represents a group of the formula $-\underset{O^-}{\underset{|}{\overset{O}{\overset{\|}{P}}}}-O-(CH_2)_2-$, $-\underset{O}{\underset{\|}{C}}-(CH_2)_n-$ or $-\underset{O}{\underset{\|}{C}}-NH-(CH_2)_n-$, n being an integer of from 2 to 10;

Y represents an ammonium group, an alkyl ammonium group having from 1 to 6 carbon atoms, a dialkylammonium or trialkylammonium group in which each alkyl group independently has from 1 to 6 carbon atoms, or a saturated or unsaturated heterocyclic group containing a quaternary nitrogen hetero atom; and

if A has the first of the values given above X^- has no value but if A has the second or third of the values given above X^- represents a

pharmaceutically acceptable anion;
or a pharmaceutically acceptable salt of such a derivative.

2. 3-Methoxy-2-(N-methyl-octadecylamino)-propanol phosphocholine.

3. 3-Methoxy-2-(N-methyl-octadecylamino)-1-[6'-(N--pyridinium)-hexanoyloxy]-propane bromide.

4. 3-Methoxy-2-(N-methyl-octadecylamino)-1-[5'-(N--pyridinium)-pentylcarbamoyloxy]-propane bromide.

5. 3-(N-Methyl-octadecylamino)-2-methoxy-propanol phosphocholine.

6. 3-(N-Methyl-octadecylamino)-2-ethoxy-propanol phosphocholine.

7. 3-Octadecylamino-2-methoxy-propanol phosphocholine.

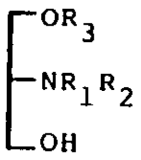
8. 3-(N-Methyl-octadecylamino)-2-methylcarbamoyloxy--propanol phosphocholine.

9. 3-(N-Methyl-octadecylamino)-2-(N,N-dimethyl--carbamoyloxy)-propanol phosphocholine.

10. 3-(N-Methyl-octadecylamino)-1-methoxy-propan-2-ol phosphocholine.

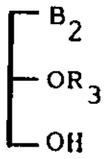
11. 1-Octadecylamino-3-methoxy-propan-2-ol phosphocholine.

12. A process for the preparation of a glycerol derivative according to claim 1, the process comprising reacting a propanol derivative of the general formula



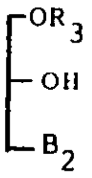
IIA

,



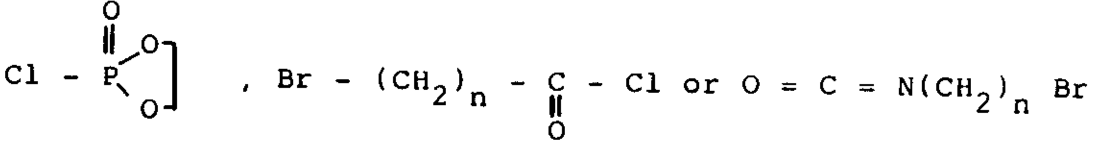
IIb

or



IIc

wherein R_1, R_2 and R_3 are as defined in claim 1 and B_2 represents a group of the formula $-NR_1'R_2$ or $-N(SO_2CH_2\emptyset)R_2$ wherein R_1' represents an alkyl group having from 1 to 5 carbon atoms, R_2 is as defined in claim 1 and $\emptyset$ represents a phenyl group with an oxo compound which has the formula



$$, \ Br-(CH_2)_n-\underset{\underset{O}{\|}}{C}-Cl \text{ or } O=C=N(CH_2)_n\ Br$$

wherein n is as defined in claim 1; the said reaction being (a) carried out in the presence of an excess of a nitrogen compound which is ammonia, an alkylamine having from 1 to 6 carbon atoms, a dialkylamine or trialkylamine in which each alkyl group independently has from 1 to 6 carbon atoms or a saturated or unsaturated heterocyclic compound containing a nitrogen hetero atom, or (b) followed by reaction of the product with one of the nitrogen compounds listed in (a); and, if the product obtained by route (a) or route (b) contains a benzylsulphonyl protected nitrogen atom, hydrogenolysing it to form a glycerol derivative I in which R_1 represents a hydrogen atom.

13. A process according to claim 12, option (a), in which the solvent for the reaction between the propanol derivative and the oxo derivative is the nitrogen compound or a mixture thereof with an aprotic solvent.

14. A process according to claim 12, option (a), or claim 13 in which the reaction is carried out at a

temperature of from 50 to 80°C.

15. A process according to claim 12, option (b), in which the reaction between the propanol derivative and the oxo derivative is carried out in an aprotic solvent.

16. A process according to claim 12, option (b), or claim 15 in which the reaction between the propanol derivative and the oxo derivative is carried out at a temperature of from -10°C to ambient temperature.

17. A process according to claim 12, option (b) or claim 15 or claim 16 in which the reaction between the propanol derivative and the oxo derivative is carried out in the presence of an organic base.

18. A process according to claim 17 in which the organic base is triethylamine.

19. A process according to claim 12, option (b) or any of claims 15 to 18 in which the reaction of the product of the first step with the nitrogen compound is carried out at a tempature of from 50 to 80°C.

20. A process according to claim 12, option (b), or any of claims 15 to 19 in which the product of the first step is reacted with a 30 to 50% stoichiometric excess of the nitrogen compound.

21. A process according to claim 12, option (b), or any of claims 15 to 19 in which the reaction of the product of the first step with the nitrogen compound is effected by heating the said product in solution in the nitrogen compound.

22. A process according to any of claims 12 to 21 in which the propanol derivative is reacted with a 10 to

100% stoichiometric excess of the oxo compound.

23. A process according to any of claims 12 to 22, which process is carried out under a non-oxidising or insert atmosphere.

24. A pharmaceutical composition comprising a glycerol derivative according to any of claims 1 to 11 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

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