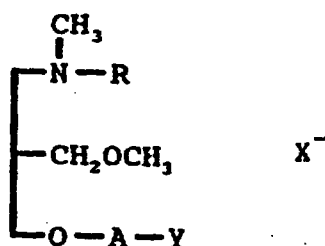


TITLE:3-(N-methyl-N-alkylamino)-2-methoxymethyl-propanolDerivativesDESCRIPTION:

The invention relates to 3-(N-methyl-N-alkylamino)-2-methoxymethyl-propanol derivatives. The invention also relates to the preparation of these derivatives and to pharmaceutical compositions containing them.

The invention provides 3-(N-methyl-N-alkylamino)-(2-methoxymethyl)-propanol derivatives of the general formula I



I

wherein R represents an alkyl group having a chain containing from 10 to 20 carbon atoms;

A represents a group of the formula $\begin{array}{c} \text{O} \\ || \\ -\text{P}-\text{O}-(\text{CH}_2)_2- \\ | \\ \text{O}^- \end{array}$,

$\begin{array}{c} \text{O} \\ || \\ -\text{C}-(\text{CH}_2)_n- \end{array}$ or $\begin{array}{c} \text{O} \\ || \\ -\text{C}-\text{NH}-(\text{CH}_2)_n- \end{array}$,

n being an integer of from 2 to 10;

Y represents an ammonium, alkylammonium, dialkylammonium, trialkylammonium, pyridinium, piperidinium, pyrrolium or pyrrolidinium group, the or each alkyl group in the alkylammonium, dialkylammonium or trialkylammonium groups having from 1 to 6 carbon atoms; and

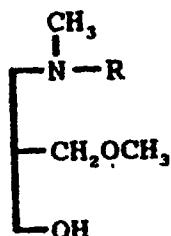
if A has the first of the values given above X⁻ has no value but if A has the second or third of the values given above X⁻ represents a pharmaceutically acceptable anion.

The invention further provides pharmaceutically acceptable salts of the derivatives I as above defined.

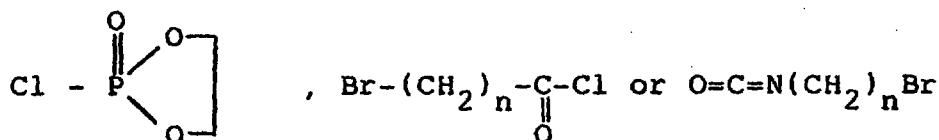
The compounds of the invention are of interest for their anti-tumour activity, which has been found to be greater than that of closely related compounds such as those described in 'Synthesis of Thioether Phosphocoline Analogues' (Eimar BOSIES, Dieter B.J. HERRMANN, Uwe BICKER, Rudi GALL and Wulf PAHIKE-LIPIDS. Vol 22 No. 11, 1987, p. 947-951).

Accordingly the invention also provides a pharmaceutical composition containing a derivative of the general formula I as above defined or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

The invention further provides a process for the preparation of a propanol derivative I as above defined, the process comprising reacting a propanol derivative of the general formula



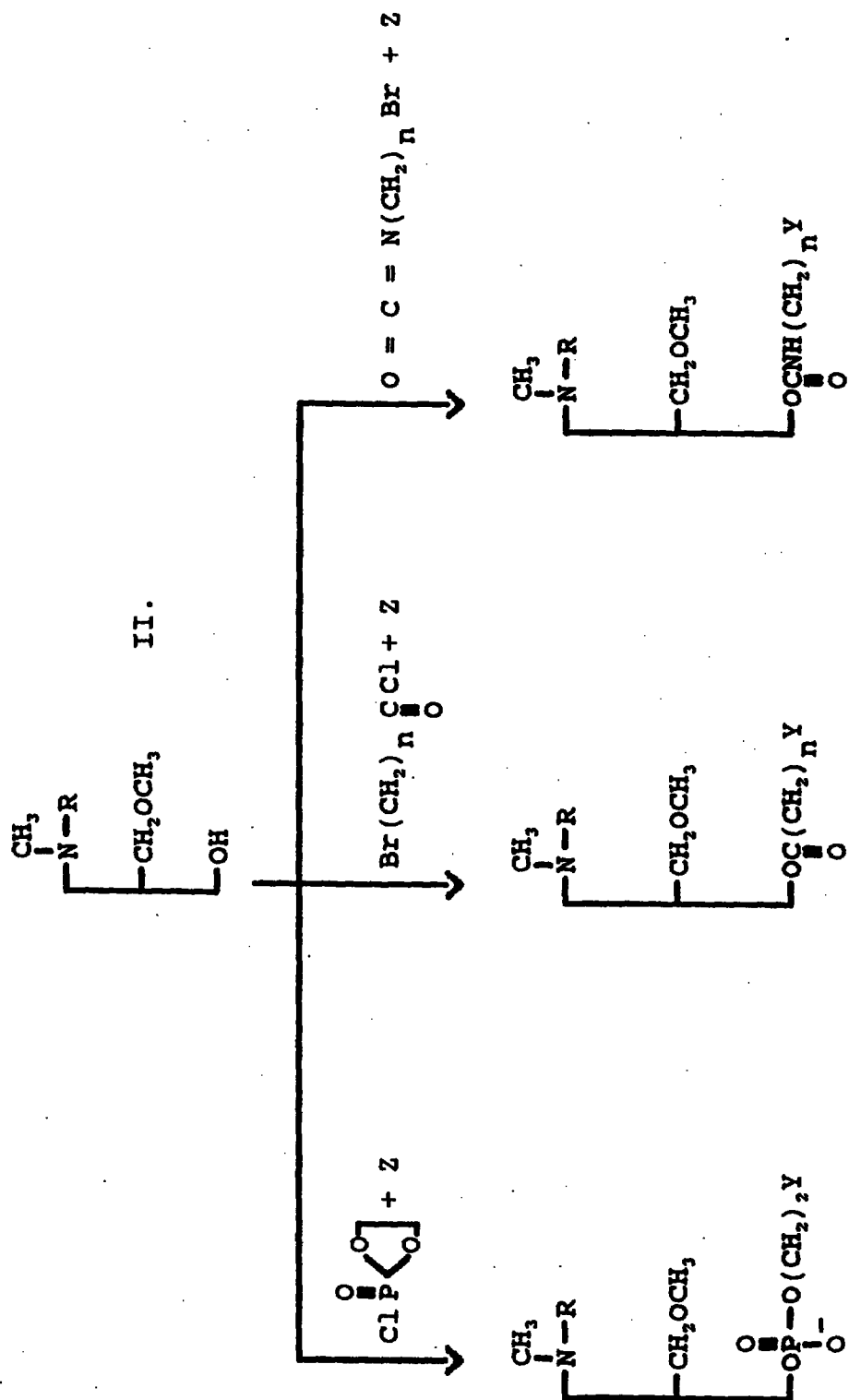
wherein R is as defined above with an oxo compound which has the formula



wherein n is as defined above; 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 in which each alkyl group independently has from 1 to 6 carbon atoms, a trialkylamine in which each alkyl group independently has from 1 to 6 carbon atoms, pyridine, piperidine, pyrrole or pyrrolidine, or (b) followed by reaction of the product with one of the nitrogen compounds listed in (a).

This process is illustrated by the following reaction scheme I in which the nitrogen compound is denoted Z.

REACTION SCHEME I



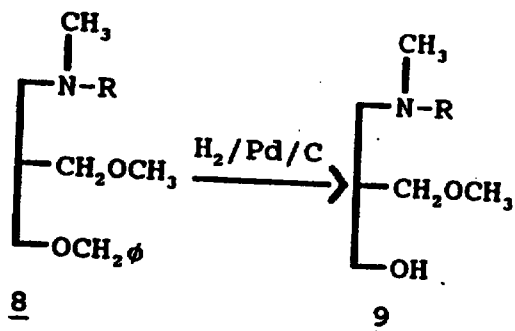
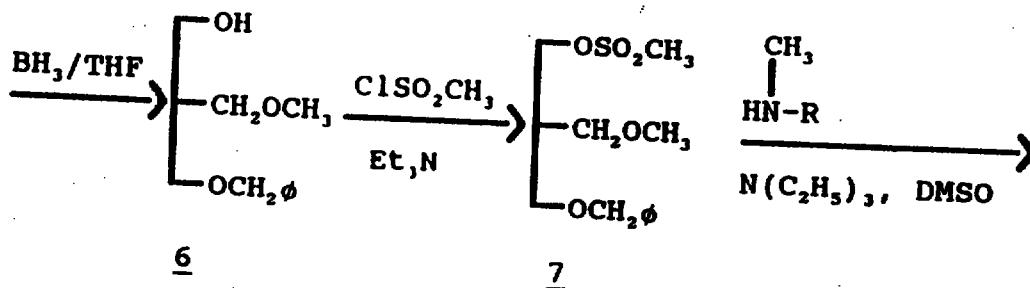
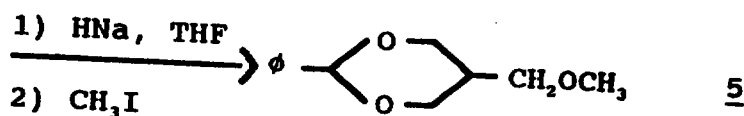
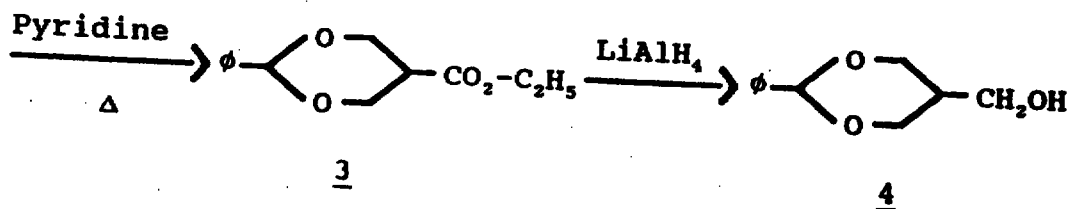
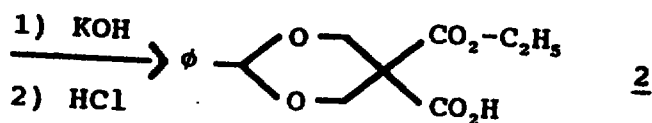
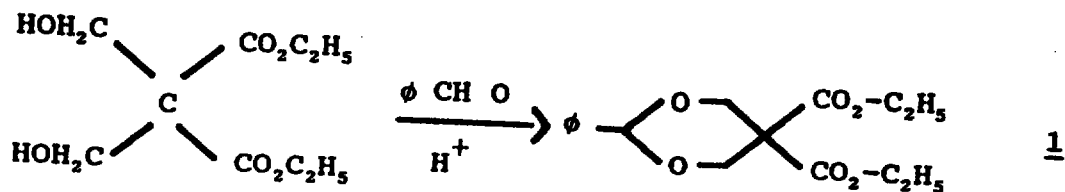
The process according to the invention may be conducted in a single step, option (a) above, or as two steps, option (b) above. In either event, it is preferably carried out under a non-oxidising or inert atmosphere such as nitrogen; and desirably the propanol derivative is reacted with a 10 to 100% stoichiometric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

The starting material II may be prepared as summarized in the following reaction scheme II and described in details in the following preparative Examples 1 to 9 wherein R stands for $\text{C}_{12}\text{H}_{25}$, $\text{C}_{16}\text{H}_{33}$ and $\text{C}_{18}\text{H}_{37}$.

REACTION SCHEME II



PREPARATIVE EXAMPLES

1. 2-Phenyl-5,5-di(ethoxycarbonyl)-1,3-dioxane 1

A mixture of diethyl bis-(hydroxymethyl)-malonate (27 gr, 0.12 mole), freshly distilled benzaldehyde (12.5 ml, 0.12 mole) and p-toluene sulfonic acid (0.2 gr) in 250 ml of dry toluene was refluxed for 3 hours using a Dean Stark apparatus. The toluene was eliminated in vacuo and the residue was distilled.

$E_{0.5}$: 170°C (29.5 gr, yield 78%)

Molecular weight = 308

IR: 1 740 cm^{-1} (C=O)

^1H NMR 60 MHz CDCl_3 , TMS

δ : 7.35 (s, 5H, ϕ); 5.4 (s, 1H, $\text{CH}\phi$); 4.8 (d, 2H); 4.2 (m, 6H, 2H + OCH_2CH_3); 1.2 (m, 6H, OCH_2CH_3)

2. 2-Phenyl-5-ethoxycarbonyl-5-carboxy-1,3-dioxane 2

25 gr of 1 (0.08 mol) were added to a solution of 6.6 gr of KOH (0.11 mol) in 140 ml ethanol. After stirring for 4 hours at room temperature, the ethanol was evaporated and the residue was treated with HCl 1 N (125 ml) at 0°C. The precipitate was filtered off, washed and dried.

21.6 gr of 2 were obtained (95%). mp 108°C

Molecular weight = 280

IR (cm^{-1}): 3400 (OH); 3100 - 3040 (ϕ); 1740 (COOEt); 1690 (COOH); 1100 (C-O-)

^1H NMR 60 MHz; CDCl_3 , TMS.

δ : 7.4 (s, 5H, ϕ); 5.5 (s, 1H, $\text{CH}\phi$); 4.9 (d, 2H, CH_2); 4.25 (m, 4H, 2H and OCH_2CH_3); 1.3 (t, 3H, OCH_2CH_3)

3. 2-Phenyl-5-ethoxycarbonyl-1,3-dioxane 3

9.2 gr (0.033 mol) of 2 in 20 ml dry-pyridine were refluxed for 5 hours. Pyridine was eliminated in vacuo, the residue was dissolved in CH_2Cl_2 , washed with water, then with brine, dried and evaporated, to give 3 (6.8 gr, 88%) mp 69°C.

Molecular weight = 236

IR: 1740 cm^{-1} (C=O)

^1H NMR, 60 MHz, CDCl_3 , TMS

δ : 7.4 (s, 5H, ϕ); 5.4 (d, 1H, $\text{CH}\phi$); 3.8 - 4.8 (m, 6H); 3.2 (m, 1H, $\text{H}-\text{C}-\text{CO}_2\text{Et}$); 1.3 (m, 3H, OCH_2CH_3).

4. 2-Phenyl-5-hydroxymethyl-1,3-dioxane 4

To a mixture of 0.62 gr of LiAlH_4 (0.016 mol) in absolute diethyl-ether (80 ml), was added, slowly, a solution of 6.8 g of 3 (0.029 mol) in 60 ml of absolute diethylether. The mixture was stirred for 4 hours at room temperature. Then, at 0°C, ethyl acetate (8 ml), water (4 ml) and NaOH 15% (4 ml) were added. The ethereal layer was decanted, dried and evaporated to afford 5.12 gr (92%) of 4, as a yellow oil. Molecular weight = 194

TLC rf: 0.5 (CH_2Cl_2) on alumina.

IR: 3430 cm^{-1} (OH)

^1H NMR 60 MHz, CDCl_3 , TMS

δ : 7.4 (s, 5H, ϕ); 5.3 (d, 1H, $\text{CH}\phi$); 4.3 - 3.2 (m, 6H); 2.2 (m, 1H, $\text{CH}-\text{CH}_2\text{OH}$); 1.3 (1H, OH)

5. 2-Phenyl-5-methoxymethyl-1,3-dioxane 5

To a mixture of HNa (50%, 1.06 gr) in 40 ml of dry THF, stirred at 0°C, a solution of 5.12 gr of 4 in 40 ml THF was added dropwise. After 30 min, CH₃I (6.6 ml) was added and the mixture was stirred at 0°C for 6 hours, then overnight at room temperature. Water was added and the mixture was extracted with diethyl-ether, the organic layer was washed with water until neutral, then with brine, dried and evaporated. The residue was purified on alumina column (eluent CH₂Cl₂) to yield 4.8 gr of 5 (86%).

Molecular weight = 208

TLC rf: 0.86 (CH₂Cl₂) alumina.

IR (cm⁻¹): 3100 - 3040 (φ), 1100 (C-O-)

¹HNMR, 60 MHz, CDCl₃, TMS

δ: 7.4 (s, 5H, φ); 5.5 (d, 1H, H—C—φ); 4.8 - 3.2 (m, 9H); 2.3 (m, 1H, CH - CH₂OMe).

6. 2-Methoxymethyl-3-benzyloxy-propanol 6

To 5 (5.4 gr, 0.026 mol) stirred at 0°C, a solution of BH₃ in THF (M, 52 ml) was added dropwise. The mixture was stirred at room temperature for 48 hours, then was quenched with cold water at 0°C and extracted with diethylether. After elimination of the solvent, the crude product was chromatographed on silicagel (eluent CH₂Cl₂, then CH₂Cl₂/MeOH 99:1) to give 6 (4 gr, 73%) as a viscous oil.

Molecular weight = 210

TLC rf: 0.24 (CH₂Cl₂) alumina

IR (cm⁻¹): 3450 (OH); 3100 - 3040 (φ); 1100 (C-O-)

¹HNMR 60 MHz, CDCl₃, TMS

δ: 7.3 (s, 5H, φ); 4.5 (s, 2H, CH₂φ); 3.1 - 3.7 (m, 10 H); 2.1 (m, 1H, CH - CH₂O-); 2.6 (1H, OH)

7. 1-Methanesulphonyloxy-2-methoxymethyl-3-benzyloxy-
propane 7

To a solution of 6 (4 gr, 0.019 mol), in a mixture of 60 ml of dry diethyl ether and 40 ml of dry CH_2Cl_2 , was added, dropwise, ClSO_2Me (2.24 ml; 0.029 mol). The mixture was stirred at room temperature for 24 hours. After extraction with CH_2Cl_2 , the organic layer was washed with brine till pH 7 and dried. The solvent was evaporated and the residue was chromatographed on silicagel (eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 99:1) to give 7 (4.6 g, 84%) as viscous oil.

Molecular weight = 288

TLC rf: 0.7 ($\text{CH}_2\text{Cl}_2/\text{MeOH}$: 95:5) silicagel

IR (cm^{-1}): 1350 (SO_2); 1170 (SO_2); 1100 (C-O-C)

$^1\text{HRMN}$ 60 MHz, CDCl_3 , TMS (δ)

4.35 (d, 2H, CH_2OSO_2); 3.3 - 3.6 (m, 7H); 3.0 (s, 3H, SO_2CH_3); 2.3 (m, 1H, $\text{CH} - \text{CH}_2\text{O}$).

The different N,N-(methyl alkyl) amines, except N,N-(octadecyl methyl)amine (Aldrich) were obtained from the corresponding alkyl halide and methyl amine according to I.G. Farbening A.G. Fr. 784,599, July 22, 1935.

8. N-Methyl-N-alkyl-2-methoxymethyl-3-benzyloxy-
-propylamine 8

7 (0.016 mol) dissolved in DMSO (15 ml) was added to a solution of N,N-(methyl alkyl)amine (0.016 mol) and Et_3N (1.4 ml) in DMSO (60 ml). The mixture was stirred at 80°C for 24 hours. After elimination of DMSO under reduced pressure, the residue was dissolved in CH_2Cl_2 , the organic phase was washed with water and dried. The crude product was chromatographed (eluent $\text{CH}_2\text{Cl}_2/\text{MeOH}$ 98:2) to give 8.

8a R = C₁₂H₂₅ (yield 50% - viscous oil)

TLC rf : 0.16 (CH₂Cl₂/MeOH 95:5)

8b R = C₁₆H₃₃ (yield 61% - viscous oil)

TLC rf : 0.18 (CH₂Cl₂/MeOH 95:5)

8c R = C₁₈H₃₇ (yield 58% - viscous oil)

TLC rf : 0.18 (CH₂Cl₂/MeOH 95:5)

IR: 1100 (C-O-) cm⁻¹

¹HNMR 60 MHz, CDCl₃, TMS

δ: 7.3 (s, 5H, φ); 4.5 (s, 2H, CH₂φ); 3.3 - 3.6 (m, 7H,

CH₃

OCH₃, 2CH₂O); 2.15 - 2.4 (m, 7H, CH₂ - N - CH₂)

1.8 (m, 1H, CH - CH₂O); 1.25 large sing. 2nH, NCH₂(CH₂)_n

CH₃; 0.9 (t, 3H, CH₃)

9. 3-(N-Methyl-N-alkylamino)-2-methoxymethyl-
-propanol 9

Obtained by hydrogenolysis of 8 in CHCl₃ with Pd/C 10%
(40 psi, 5 hours at 40°C).

9a R = C₁₂H₂₅ (yield 79%)

TLC rf : 0.36 (CH₂Cl₂/MeOH 90:10)

9b R = C₁₆H₃₃ (yield 87%)

TLC rf : 0.39 (CH₂Cl₂/MeOH 90:10)

9c R = C₁₈H₃₇ (yield 85%)

TLC rf : 0.39 (CH₂Cl₂/MeOH 90:10) Molecular weight = 385

IR (cm⁻¹): 3450 (OH) ; 1100 (C-O-C)

¹HNMR, 60 MHz, CDCl₃, TMS

δ: 5.3 (1H, OH); 3.3 - 3.8 (m, 7H, OCH₃, 2 CH₂O)

2.7 (m, 7H, NCH₃ and CH₂-N-CH₂); 2.2 (m, 1H, CH-CH₂O); 1.25

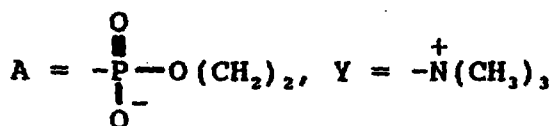
large sing, 2nH, NCH₂(CH₂)_nCH₃; 0.9 (t, 3H, CH₃)

The invention is illustrated by the following Examples.

Example 10:

3-(N-Methyl-N-alkylamino)-2-methoxymethyl-propanol
phosphocholine

Alkyl stands for $-C_{12}H_{25}$, $-C_{16}H_{33}$ and $-C_{18}H_{37}$



To a cooled (5°C), stirred solution of 9 (7 mmol) and 3 ml of NEt_3 in dry benzene (20 ml), was added 2-chloro 2-oxo 1,3,2-dioxaphospholane (2 gr, 14 mmol) in 4 ml of C_6H_6 , 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 gaseous 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 silicagel (eluent $\text{CHCl}_3/\text{MeOH}$ 90:10; 70:30; 30:70 then MeOH) to yield the title compound.

10a $R = C_{12}H_{25}$ (yield 40%) $\text{MH}^+ = 467$
TLC rf : 0.25 ($\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ 70:30:7)

10b $R = C_{16}H_{33}$ (yield 44%) $\text{MH}^+ = 523$
TLC rf : 0.26 ($\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ 70:30:7)

10c $R = C_{18}H_{37}$ (yield 45%) $\text{MH}^+ = 551$
TLC rf : 0.26 ($\text{CHCl}_3/\text{MeOH}/\text{NH}_4\text{OH}$ 70:30:7)

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

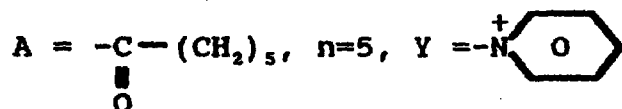
^1H NMR, 500 MHz, CH_3OD , TMS

δ : 0.85 (t, 3H, CH_3); 1.2 [large sing, 2nH, $(\text{CH}_2)_n$]; 1.45 (m, 2H, NCH_2CH_2); 2.0 (m, 1H, $\text{CH}-\text{CH}_2\text{O}$); 2.15 (s, 3H, NCH_3); 2.3 (m, 4H, $\text{CH}_2-\text{N}-\text{CH}_2$); 3.15 [s, 9H, $\text{N}^+(\text{CH}_3)_3$]; 3.35 (s, 3H, OCH_3); 3.4 (d, 2H, CH_2-OCH_3); 3.55 (m, 2H, CH_2N^+); 3.85 (m, 2H, CH_2OP); 4.25 (m, 2H, POCH_2).

Example 11:

3-(N-Methyl-N-alkylamino)-2-methoxymethyl-1-[6-(N-pyridinium)-hexanoyloxy]-propane bromide

Alkyl stands for $-\text{C}_{12}\text{H}_{25}$, $-\text{C}_{16}\text{H}_{33}$ and $-\text{C}_{18}\text{H}_{37}$



A solution of 9 (9 mmol) and triethylamine (25 mmol) in 15 ml of ethanol-free trichloromethane, were added dropwise to a solution of 10 mmol of 5-bromohexanoyl chloride in 10 ml of the same solvent at 0°C under nitrogen circulation. The mixture was then stirred for about 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 nitrogen circulation for 24 hours. Pyridine was eliminated in vacuo and the residue was purified by column chromatography (eluent CHCl_3 , then $\text{CHCl}_3/\text{MeOH}$ 90:10) to yield the title compound.

11a R = $\text{C}_{12}\text{H}_{25}$ (yield 68%)

11b R = $\text{C}_{16}\text{H}_{33}$ (yield 60%)

11c R = $\text{C}_{18}\text{H}_{37}$ (yield 71%)

IR (cm^{-1}): 1100 (C-O-C); 1740 (C=O); 1640 (pyridine)

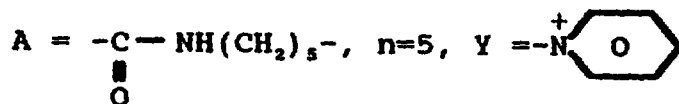
^1H NMR, 500 MHz, CDCl_3 , TMS

δ : 0.85 (t, 3H, CH_3); 1.2 [large sing, 2nH, $(\text{CH}_2)_n$]; 2.2 (s, 3H, NCH_3); 2.35 [t, 2H, $\text{C}(\text{O})\text{CH}_2$]; 3.35 (s, 3H, OCH_3); 3.45 (d, 2H, CH_2-OCH_3)

Example 12:

3-(N-Methyl-N-alkylamino)-2-methoxymethyl-1-[5-(N-pyridinium)-pentylcarbamoyloxy]-propane bromide

Alkyl stands for $-C_{12}H_{25}$, $-C_{16}H_{33}$ and $-C_{18}H_{37}$



A mixture of 9 (9 mmol), 5-bromopentylisocyanate (12 mmol) in benzene 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 (CHCl_3 , then $\text{CHCl}_3/\text{MeOH}$, 95:5, 90:10) to give the title compound.

12a R = $C_{12}H_{25}$ (yield 49%)

12b R = $C_{16}H_{33}$ (yield 52%)

12c R = $C_{18}H_{37}$ (yield 62%)

IR (cm^{-1}): 1100 (C-O-C); 1640 (pyridine) 1720 (CONH); 3350 (NH)

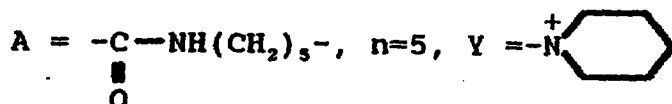
^1HMR , 500 MHz, CDCl_3 , TMS

δ : 0.90 (t, 3H, CH_3); 1.2 [large sing, 2nH, $(\text{CH}_2)_n$]; 2.15 (s, 3H, NCH_3); 3.25 [t, 2H, $\text{C}(\text{O})\text{NHCH}_2$]; 3.35 (s, 3H, OCH_3); 3.4 (d, 2H, $\text{CH}_2\text{-OCH}_3$); 5.1 (t, 2H, CH_2N); 5.6 (d, 1H, NH)

Example 13:

3-(N-Methyl-N-alkylamino)-2-methoxymethyl-1-[5-(N-piperidinium)-pentylcarbamoyloxy]-propane bromide

Alkyl stands for $-C_{12}H_{25}$, $-C_{16}H_{33}$ and $-C_{18}H_{37}$



This compound is prepared by the same process as described in example 12, but using piperidine instead of pyridine.

13a R = C₁₂H₂₅ (yield 49%)

13b R = C₁₆H₃₃ (yield 42%)

13c R = C₁₈H₃₇ (yield 53%)

IR (cm⁻¹): 1100 (C-O-C); 1720 (CONH); 3350 (NH)

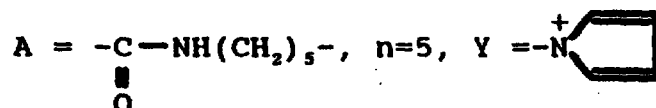
¹HNMR, 500 MHz, CDCl₃, TMS

δ: 0.85 (t, 3H, CH₃); 1.2 [large sing, 2nH, (CH₂)_n]; 2.15 (s, 3H, NCH₃); 3.25 [t, 2H, C(O)NHCH₂]; 3.35 (s, 3H, OCH₃); 3.4 (d, 2H, CH₂-O-CH₃); 5 (t, 2H, CH₂N); 5.6 (d, 1H, NH)

Example 14:

3-(N-Methyl-N-alkylamino)-2-methoxymethyl-1-[5-(N-pyrrolium)-pentylcarbamoyloxy]-propane bromide

Alkyl stands for -C₁₂H₂₅, -C₁₆H₃₃ and -C₁₈H₃₇



This compound is prepared by the same process as described in example 12, but using pyrrole instead of pyridine.

14a R = C₁₂H₂₅ (yield 53%)

14b R = C₁₆H₃₃ (yield 61%)

14c R = C₁₈H₃₇ (yield 48%)

IR (cm⁻¹): 1100 C-O-C); 1720 (CONH); 3350 (NH)

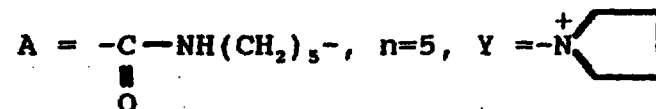
¹HNMR, 500 MHz, CDCl₃, TMS

δ: 0.85 (t, 3H, CH₃); 1.2 [large sing, 2nH, (CH₂)_n]; 2.2 (s, 3H, NCH₃); 3.25 [t, 2H, C(O)NHCH₂]; 3.35 (s, 3H, OCH₃); 3.4 (d, 2H, CH₂-O-CH₃); 5 (t, 2H, CH₂N); 5.6 (d, 1H, NH)

Example 15:

3-(N-Methyl-N-alkylamino)-2-methoxymethyl-1-[5-(N-pyrrolidinium)-pentylcarbamoyloxy]-propane bromide

Alkyl stands for -C₁₆H₃₃, -C₁₇H₃₅ and -C₁₈H₃₇



This compound is prepared by the same procedure as described in example 12, but using pyrrolidine instead of pyridine.

15a R = C₁₂H₂₅ (yield 49%)

15b R = C₁₆H₃₃ (yield 45%)

15c R = C₁₈H₃₇ (yield 56%)

IR(cm⁻¹): 1100 (C-O-C); 1720 (CONH); 3350 (NH)

¹HNMR, 500 MHz, CDCl₃, TMS

δ: 0.85 (t, 3H, CH₃); 1.2 [large sing, 2nH, (CH₂)_n]; 2.15 (s, 3H, NCH₃); 3.25 [t, 2H, C(O)NHCH₂]; 3.35 (s, 3H, OCH₃); 3.4 (d, 2H, CH₂-O-CH₃); 5 (t, 2H, CH₂N); 5.6 (d, 1H, NH)

Toxicity

The toxicity of the compounds of the invention, has been determined per os on mice, by usual methods. Their LD₅₀ 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 one of the first related compounds discovered as inhibiting the neoplastic cell-growth: the 1-0-octadecyl- 2-0-methylglycero- 3-phosphocholine (ET18OCH₃, or methoxy PAF ; Andreesen, 1988).

For this study, a lung carcinoma cell line, called A.427, have been used; they are anchorage-dependent cells.

The A.427 cells were grown in EMEM medium containing sodium pyruvate and non-essential amino acids (Flow Labs), supplemented with 10% foetal bovine serum (FBS; Gibco). The growth media contain 100 U/ml of penicillin and 100 μ g/ml of streptomycin (Flow Labs).

The compounds of the invention and the reference compound ET18OCH₃, (Bachem; Switzerland) 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 A.427. To carry out this study, $1 \cdot 10^3$ A.427 cells, previously treated with the compounds of the invention for 24 hours, were seeded into 25 cm² 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:

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

and summarized in the following table.

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 $\pm$ 2.2
ET18OCH ₃	33.4 $\pm$ 1.5
EX 10 - a	27.1 $\pm$ 2.6 **
EX 10 - b	21.4 $\pm$ 1.8 *
EX 10 - c	14.2 $\pm$ 0.9 ***
EX 11 - a	23.2 $\pm$ 2.4 *
EX 11 - b	18.5 $\pm$ 2.1 *
EX 12 - a	25.6 $\pm$ 3.1 **

COMPOUNDS	P.E. (%)
EX 12 - b	20.2 $\pm$ 2.3 **
EX 13 - b	19.1 $\pm$ 3.6 ***
EX 13 - c	17.6 $\pm$ 2.7 *
EX 14 - a	22.7 $\pm$ 3.1 *
EX 14 - b	27.3 $\pm$ 3.3 *
EX 14 - c	18.6 $\pm$ 2.7 **
EX 15 - b	21.7 $\pm$ 3.3 **
EX 15 - c	26.4 $\pm$ 2.6 **

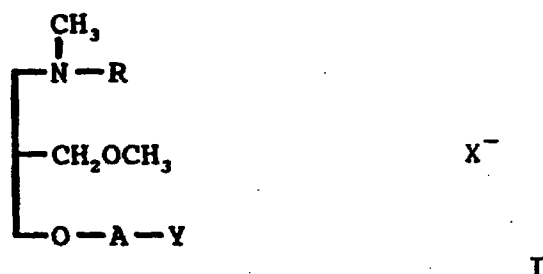
The statistical symbols refer to the comparison between each example with the reference ET18OCH₃. The different symbols: NS, *, ** and *** mean that the result is respectively not significative, significative, very significative and highly significative.

Posology

In human therapy, the compounds of the invention are preferably administered by I.V. route. Usual posology is from 2.5 to 5 mg/dm² of the tumour under treatment per diem, three to six days per month in slow perfusion.

CLAIMS:

1. A 3-(N-methyl-N-alkylamino)-2-methoxymethyl-propanol derivative of the general formula I:



wherein

R represents an alkyl group having a chain containing from 10 to 20 carbon atoms;

A represents a group of the formula $-\text{P}(=\text{O})(\text{O}-)(\text{O}-)(\text{CH}_2)_2-$,

$-\text{C}(=\text{O})(\text{CH}_2)_n-$ or $-\text{C}(=\text{O})\text{NH}(\text{CH}_2)_n-$, n being an integer of

from 2 to 10;

Y represents an ammonium, alkylammonium, dialkylammonium, trialkylammonium, pyridinium, piperidinium, pyrrolium or pyrrolidinium group, the or each alkyl group in the alkylammonium, dialkylammonium or trialkylammonium groups having from 1 to 6 carbon atoms; 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.

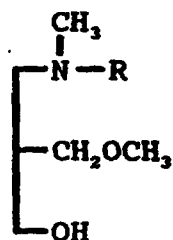


2. 3-(N-Methyl-N-decylamino)-2-methoxymethyl-propanol phosphocholine.
3. 3-(N-Methyl-N-hexadecylamino)-2-methoxymethyl-propanol phosphocholine.
4. 3-(N-Methyl-N-octadecylamino)-2-methoxymethyl-propanol phosphocholine.
5. 3-(N-Methyl-N-decylamino)-2-methoxymethyl-1-[6-(N-pyridinium)-hexanoyloxy]-propane bromide.
6. 3-(N-Methyl-N-hexadecylamino)-2-methoxymethyl-1-[6-(N-pyridinium)-hexanoyloxy]-propane bromide.
7. 3-(N-Methyl-N-octadecylamino)-2-methoxymethyl-1-[6-(N-pyridinium)-hexanoyloxy]-propane bromide.
8. 3-(N-Methyl-N-decylamino)-2-methoxymethyl-1-[5-(N-pyridinium)-pentylcarbamoyloxy]-propane bromide.
9. 3-(N-Methyl-N-hexadecylamino)-2-methoxymethyl-1-[5-(N-pyridinium)-pentylcarbamoyloxy]-propane bromide.
10. 3-(N-Methyl-N-octadecylamino)-2-methoxymethyl-1-[5-(N-pyridinium)-pentylcarbamoyloxy]-propane bromide.
11. 3-(N-Methyl-N-decylamino)-2-methoxymethyl-1-[5-(N-piperidinium)-pentylcarbamoyloxy]-propane bromide.
12. 3-(N-Methyl-N-hexadecylamino)-2-methoxymethyl-1-[5-(N-piperidinium)-pentylcarbamoyloxy]-propane bromide.
13. 3-(N-Methyl-N-octadecylamino)-2-methoxymethyl-1-[5-(N-piperidinium)-pentylcarbamoyloxy]-propane bromide.
14. 3-(N-Methyl-N-decylamino)-2-methoxymethyl-1-[5-(N-pyrrolidium)-pentylcarbamoyloxy]-propane bromide.

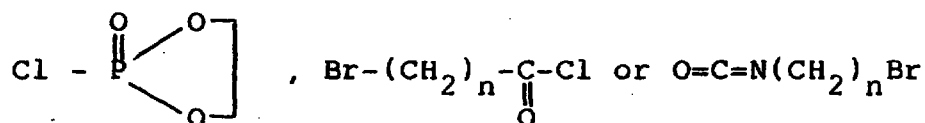


15. 3-(N-Methyl-N-hexadecylamino)-2-methoxymethyl-1-[5-(N-pyrrolium)-pentylcarbamoyloxy]-propane bromide.
16. 3-(N-Methyl-N-octadecylamino)-2-methoxymethyl-1-[5-(N-pyrrolium)-pentylcarbamoyloxy]-propane bromide.
17. 3-(N-Methyl-N-decylamino)-2-methoxymethyl-1-[5-(N-pyrrolidinium)-pentylcarbamoyloxy]-propane bromide.
18. 3-(N-Methyl-N-hexadecylamino)-2-methoxymethyl-1-[5-(N-pyrrolidinium)-pentylcarbamoyloxy]-propane bromide.
19. 3-(N-Methyl-N-octadecylamino)-2-methoxymethyl-1-[5-(N-pyrrolidinium)-pentylcarbamoyloxy]-propane bromide.

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



wherein R is as defined in claim 1 with an oxo compound which has the formula



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 in which each alkyl group independently has from 1 to 6 carbon atoms, a trialkylamine in which each alkyl group independently has from 1 to 6 carbon atoms, pyridine, piperidine, pyrrole or pyrrolidine, or (b) followed by reaction of the product with one of the nitrogen compounds listed in (a).



21. A process according to claim 20, 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.

22. A process according to claim 20, option (a), or claim 21 in which the reaction is carried out at a temperature of from 50 to 80°C.

23. A process according to claim 20, option (b), in which the reaction between the propanol derivative and the oxo derivative is carried out in an aprotic solvent.

24. A process according to claim 20, option (b), or claim 23 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.

25. A process according to claim 20, option (b) or claim 23 or claim 24 in which the reaction between the propanol derivative and the oxo derivative is carried out in the presence of an organic base.

26. A process according to claim 25 in which the organic base is triethylamine.

27. A process according to claim 20, option (b) or any of claims 23 to 26 in which the reaction of the product of the first step with the nitrogen compound is carried out at a temperature of from 50 to 80°C.

28. A process according to claim 20, option (b), or any of claims 23 to 27 in which the product of the first step is reacted with a 30 to 50% stoichiometric excess of the nitrogen compound.



29. A process according to claim 20, option (b), or any of claims 23 to 27, 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.

30. A process according to any of claims 20 to 29 in which the propanol derivative is reacted with a 10 to 100% stoichiometric excess of the oxo compound.

31. A process according to any of claims 20 to 30, which process is carried out under a non-oxidising or inert atmosphere.

32. A pharmaceutical composition comprising a propanol derivative according to any of claims 1 to 19 or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.
