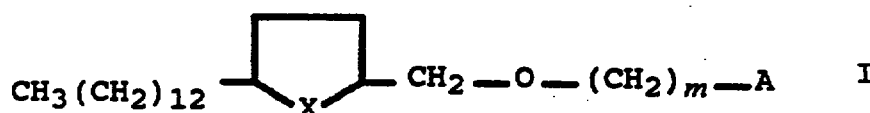


TITLE:Derivatives of Tetrahydrofuran and Tetrahydrothiophen**DESCRIPTION:**

The invention relates to derivatives of tetrahydrofuran and tetrahydrothiophen, to a process for their preparation, and to pharmaceutical compositions containing them.

The invention provides derivatives of tetrahydrofuran and tetrahydrothiophen, which derivatives have the general formula I

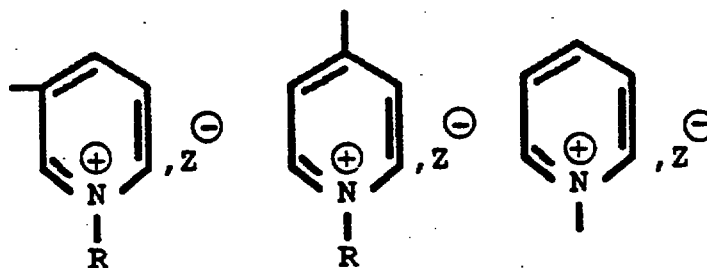


wherein

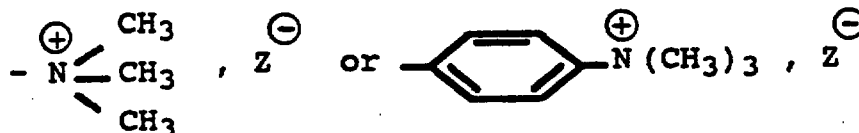
X represents an oxygen or sulphur atom,

m is an integer of from 1 to 12, and

either A represents a pyridinium salt of the formula:



wherein R represents a hydrogen or a methyl group and Z^- represents a pharmaceutically acceptable anion, or A represents an ammonium salt of the formula:

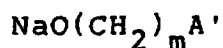


wherein Z^- is as above defined.

The invention includes these compounds in the form of their separated stereoisomers or of any mixture of the same.

The compounds of the invention are of interest as anti-PAF agents (PAF means platelets aggregation factor). They possess anti-anaphylactic, anti-thrombotic and anti-ischemic activity, are immunodepressors and act also against immune alteration of kidney, against various shocks, against skin allergies and intestinal ulcers induced by endotoxine for instance.

The invention further provides a process for the preparation of the compounds according to the invention, which process comprises condensing 5-tridecyl-2-methylsulphonyloxymethyl-tetrahydrofuran or 5-tridecyl-2-methylsulphonyloxymethyl-tetrahydrothiophen with a compound of the general formula



wherein m is as above defined and A' represents any of the groups A as above defined or a 3-pyridyl, 4-pyridyl, dimethylamino or 4-dimethylaminophenyl group; and, if A' represents a 3-pyridyl or 4-pyridyl group, then quaternizing or salifying the nitrogen atom in the product by reaction with an excess of a compound R wherein R and Z are as above defined; and, if A' represents a dimethylamino or 4-dimethylaminophenyl group, then quaternizing the nitrogen atom in the product by reaction with an excess of a compound CH_3Z wherein Z is as above defined.

The condensation is suitably carried out in solvent such as dimethylformamide at a temperature of from 60 to 80°C. The quaternizations, if necessary, may be carried out under the conditions usually used for such reactions.

5-Tridecyl-2-methylsulphonyloxymethyl-tetrahydrofuran and 5-tridecyl-2-methylsulphonyloxymethyl-tetrahydrothiophen may be prepared by reacting 5-tridecyl-tetrahydrofurfuryl alcohol or 5-tridecyl-tetrahydrothenyl alcohol respectively with methylsulphonyl chloride in benzene or pyridine, working up by conventional methods.

The compound $\text{NaO}(\text{CH}_2)_m\text{A}'$ may be prepared from the corresponding alcohol $\text{HO}(\text{CH}_2)_m\text{A}'$ by reaction with sodium hydride in dimethylformamide at from 50° to 60°C.

EXAMPLE 1

2-(5-tridecyl-tetrahydrofurfuryloxy)-ethyl trimethyl
ammonium iodide

X = 0, m = 2, A = - N[⊕](CH₃)₃, I

Step a: Preparation of 5-tridecyl-2-(2-dimethylamino-ethoxymethyl)-tetrahydrofuran. A = (CH₂)₂N(CH₃)₂

To 1.13 g (12.7 mmoles) of 2-dimethylamino-ethanol in 100 ml of dry dimethylformamide was added 0.51 g (12.7 mmoles) of sodium hydride (60% dispersion in oil). The mixture was heated for 30 minutes at 60°C with stirring, and then 2.3 g (6.35 mmoles) of 5-tridecyl-2-methylsulphonyloxymethyl-tetrahydrofuran were added. After heating for another 2 hours at 80°C with stirring, the mixture was cooled and the excess sodium hydride was decomposed by addition of 5 ml of methanol. Evaporation of the greater part of the dimethylformamide lead to a residue which was diluted with water and extracted three times with diethyl ether. The organic layer was washed with water until neutrality, dried over anhydrous magnesium sulphate and evaporated in vacuo. The crude title compound was then purified by chromatography on silica gel using 1% to 5% methanol in chloroform as eluent to yield 0.9 g (40% as an oil).

IR (film) : 2930, 2860 (C-H), 2780 (N-CH₃), 1120 (C-O-C) cm⁻¹,
¹HNMR (80 MHz, CDCl₃, HMDS) δ : 3.95 (m, 2H, CH-O), 3.58 (t, 2H, OCH₂-C-N), 3.42 (d, 2H, CH₂-O), 2.5 (t, 2H, CH₂N), 2.25 (s, 6H, N(CH₃)₂), 2.06-1.35 (m, 6H, CH₂-C-O), 1.22 (large s, 22H, (CH₂)₁₁), 0.82 (t, 3H, CH₃).

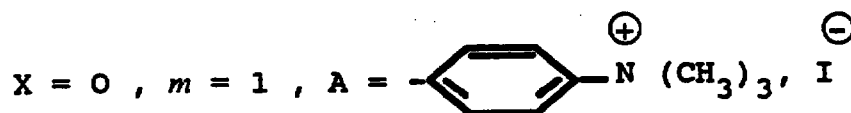
Step b: Preparation of 2-(5-tridecyl-tetrahydrofurfuryloxy)-ethyl trimethyl ammonium iodide.

0.5 g (1.4 mmoles) of the compound prepared in step a) above and an excess of methyl iodide (2 g, 14 mmoles) in 50 ml of dry acetone were stirred for 2 hours at room temperature. After elimination of the solvent and of the excess methyl iodide, the residue was chromatographed on a silica gel column using 5% to 20 methanol in chloroform as eluent leading to the title compound as a yellow solid, mp = 104°C.

IR (KBr) 2940, 2860 (C-H), 1120, 1070 (C-O-C) cm⁻¹. ¹HNMR (80 MHz, CDCl₃, HMDS) δ : 4.00 (m, 5H, CH₂-O + O-CH-C-O), 3.77 (m, 3H, CH-O + CH₂N[⊕]), 3.56 (s, 9H, N(CH₃)₃[⊕]), 2.25-1.50 (m, 6H, CH₂-C-O), 1.25 (large s, 22H, (CH₂)₁₁), 0.85 (t, 3H, CH₃).

EXAMPLE 2

4-(5-tridecyl-tetrahydrofurfuryloxymethyl)-N,N,N-trimethyl-anilinium iodide



This preparation was conducted as described in Example 1, but using p-dimethylaminobenzyl alcohol in place of 2-dimethylamino-ethanol. The p-dimethylamino-benzyl alcohol had been prepared by reduction of commercial

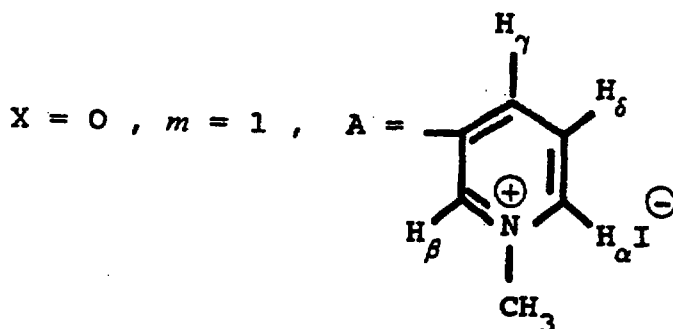
p-dimethylaminobenzaldehyde with sodium borohydride in ethanol. The title compound was obtained as a yellow solid, mp = 124-126°C.

IR (KBr) : 3000 (aromatic C-H), 2910, 2820 (C-H), 1100, 1080 (C-O-C) cm^{-1} .

^1H NMR (80 MHz, CDCl_3 , HMDS) δ : 8.07 (m, 2H, $\text{CH}=\text{C}-\text{N}^+$), 7.66 (m, 2H, $\text{CH}=\text{C}-\text{C}$), 4.65 (s, 2H, $\text{O}-\text{CH}_2-\phi$), 4.05 (large s, 11H, N^+ $(\text{CH}_3)_3$ + $\text{CH}-\text{O}$), 3.49 (d, 2H, $\text{OCH}_2-\text{C}-\text{O}$), 2.12-1.42 (m, 6H, $\text{CH}_2-\text{C}-\text{O}$), 1.22 (large s, 22H, $(\text{CH}_2)_{11}$), 0.82 (t, 3H, CH_3).

EXAMPLE 3

3-(5-tridecyl-tetrahydrofurfuryloxymethyl)-N-methyl-pyridinium iodide



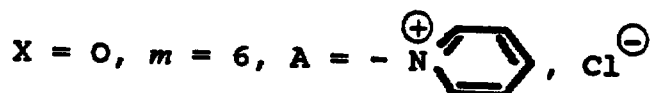
This preparation was conducted as described in Example 1, but using 3-hydroxymethyl-pyridine in place of 2-dimethyl-amino-ethanol. The title compound was obtained as a yellow solid. mp: 76°C.

IR (KBr), 3080, 3060 (aromatic C-H), 2940, 2870 (C-H), 1645 cm^{-1} ($\text{C}=\text{N}^+$), 1130, 1080 (C-O-C) cm^{-1} .

^1H NMR (80 MHz, CDCl_3 , HMDS) δ : 9.38 (d, 1H, H_α), 9.26 (s, 1H, H_β), 8.57 (d, 1H, H_γ), 8.17 (t, 1H, H_δ), 4.90 (s, 2H, $\text{O}-\text{CH}_2$ -pyridine), 4.68 (s, 3H, CH_3-N^+), 4.36-3.72 (m, 2H, $\text{CH}-\text{O}$), 3.62 (d, 2H, $\text{O}-\text{CH}_2-\text{C}-\text{O}$), 2.21 - 1.55 (m, 6H, $\text{CH}_2-\text{C}-\text{O}$), 1.25 (large s, 22H, $(\text{CH}_2)_{11}$), 0.82 (t, 3H, CH_3).

EXAMPLE 4

N-[6-(5-tridecyl-tetrahydrofurfuryloxy)-hexyl]-pyridinium chloride



This preparation was conducted as described in Example 1, step (a) only, but using 6-pyridinium-hexanol chloride instead of 2-dimethylamino-ethanol. The title compound was obtained as a hygroscopic oil. $^1\text{HNMR}$ (80MHz, CDCl_3 HMDS)

δ : 9.55 (d, 2H, $\text{CH}=\text{N}^{\oplus}$), 8.55 (m, 1H, $\text{N}^{\oplus} \text{C}_5\text{H}_5$ -H) ,

8.17 (t, 2H, $\text{CH}=\text{C}-\text{N}^{\oplus}$), 4.97 (m, 2H, $\text{CH}_2\text{N}^{\oplus}$), 4.47 - 3.67 (m, 4H, $\text{CH}-\text{O}+\text{O}-\text{CH}_2-\text{C}-\text{O}$), + 3.33 (m, 2H, CH_2O), 2.2 - 1.32 (m, 10 H, $\text{CH}_2-\text{C}-\text{O} + \text{CH}_2-\text{C}-\text{N}$), 1.2 (large s, 26H, $(\text{CH}_2)_{11} + \text{O}-\text{C}_2-(\text{CH}_2)_2-\text{C}_2-\text{N}^{\oplus}$), 0.82 (t, 3H, CH_3).

TOXICOLOGY

The compounds of the invention have been administered to mice for determination of acute LD_{50} . For all the compounds of the invention LD_{50} was over 300 mg/kg (IP or SC) and 600 mg/kg (PO).

PHARMACOLOGY

A proof of the pharmaceutical interest of the compounds of the invention has been established by the following pharmaceutical experimentation.

Inhibition of the platelets aggregation of New Zealand rabbits

The experimentation was conducted on platelets with plasma of New Zealand rabbits. Blood samples were taken from the auricular artery and placed in a citrate buffer (3.8% pH 7.4); blood was further centrifuged for 15 minutes at 1200 RPM. The tested sample was prepared in dimethyl-

sulphoxide (DMSO), then poured on platelets rich plasma for 1 minute, then a dose of 2.5 nM of PAF was added.

The determination is made on a Cronolog Coultronics apparatus which determines the transmission percentage corresponding to the maximum height of the peak before the desaggregation. The percentage of variation of the inhibition with respect to the transmission percentage is calculated (control : pure DMSO).

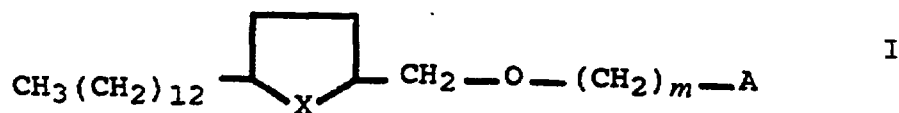
This method was described in detail in LABORATORY INVESTIGATIONS, Vol 41, No. 3, p. 275, 1979, JEAN-PIERRE CAZENAVE, Dr. MED., JACQUES BENVENISTE, Dr. MED., AND J. FRASER MUSTARD, M.D., "Aggregation of Rabbits Platelets by Platelet-Activating Factor Is Independent of the Release Reaction and the Arachidonate Pathway and Inhibited by Membrane-Active Drugs".

The results demonstrate that the compounds inhibit the aggregation induced by 2.5 nM of PAF. Five tests made on 5 different rabbits allowed the calculation of the IC_{50} of the various compounds using the linear regression test. These values were:

compound of Example 1	:	2.66	$\cdot 10^{-5}$
compound of Example 2	:	1.27	$\cdot 10^{-5}$
compound of Example 3	:	1.1	$\cdot 10^{-5}$
compound of Example 4	:	2.8	$\cdot 10^{-6}$

**CLAIMS:**

1. A derivative of tetrahydrofuran or tetrahydrothiophen, which derivative has the general formula I

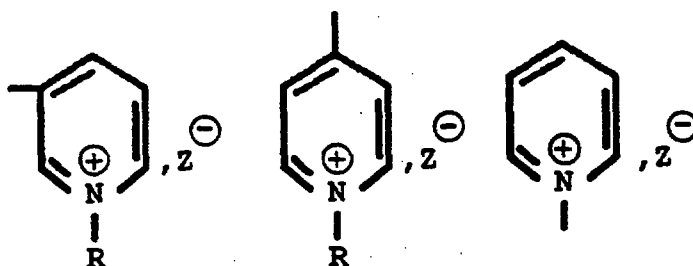


wherein

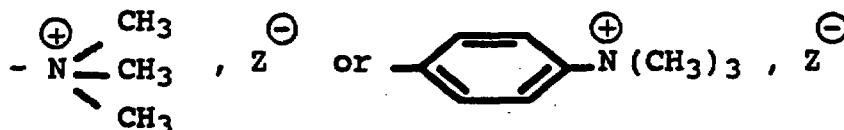
X represents an oxygen or sulphur atom,

m is an integer of from 1 to 12, and

either A represents a pyridinium salt of the formula:



wherein R represents a hydrogen or a methyl group and Z^- represents a pharmaceutically acceptable anion, or A represents an ammonium salt of the formula:



wherein Z^- is as above defined.

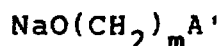
2. 2-(5-Tridecyl-tetrahydrofurfuryloxy)-ethyl trimethyl ammonium iodide.
3. 4-(5-Tridecyl-tetrahydrofurfuryloxymethyl)-N,N,N-trimethyl-anilinium iodide.



4. 3-(5-Tridecyl-tetrahydrofurfuryloxymethyl)-N-methyl-pyridinium iodide.

5. N-[6-(5-Tridecyl-tetrahydrofurfuryloxy)-hexyl]-pyridinium chloride.

6. A process for the preparation of a derivative according to claim 1, the process comprising condensing 5-tridecyl-2-methylsulphonyloxymethyl-tetrahydrofuran or 5-tridecyl-2-methylsulphonyloxymethyl-tetrahydrothiophen with a compound of the general formula



wherein m is as defined in claim 1 and A' represents any of the groups A as defined in claim 1 or a 3-pyridyl, 4-pyridyl, dimethylamino or 4-dimethylaminophenyl group; and, if A' represents a 3-pyridyl or 4-pyridyl group, then quaternizing or salifying the nitrogen atom in the product by reaction with an excess of a compound R wherein R and Z are as defined in claim 1; and, if A' represents a dimethylamino or 4-dimethylaminophenyl group, then quaternizing the nitrogen atom in the product by reaction with an excess of a compound CH_3Z wherein Z is as defined in claim 1.

7. A process according to claim 6 in which the condensation is carried out in dimethylformamide at a temperature of from 60° to 80°C.

8. A pharmaceutical composition comprising a derivative according to claim 1 in admixture with a pharmaceuticallaly acceptable diluent or carrier.