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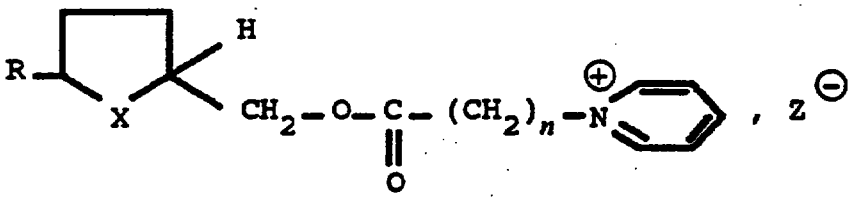
TITLE:

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



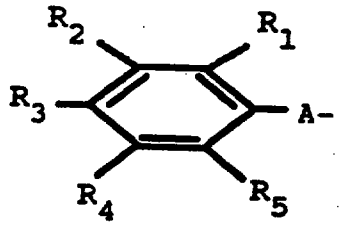
I

wherein

X represents an oxygen or sulphur atom,

n is an integer of from 1 to 6,

R represents a straight chain or branched chain alkyl group having from 1 to 13 carbon atoms, a cycloalkyl group having from 5 to 10 carbona toms, or a group of the formula



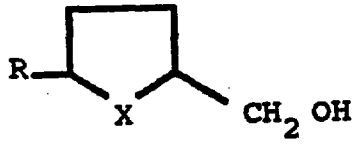
wherein each of R_1, R_2, R_3, R_4 and R_5 independently represents a hydrogen atom or a methyl or methoxy group and A represents a valence bond or an alkyl group having from 1 to 5 carbon atoms, and

$Z^{\ominus}$ represents a pharmaceutically acceptable anion.

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

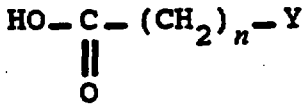
The compounds of the invention are of interest as anti-PAF agents (PAF means platelets aggregation factor). They possess anti-anaphylatic, anti-thrombotic and anti-ischemic activity, are immunodepressors and act also against immune alteration of kidney, against various shocks, against skin allergies and intestinal ulcers induced by endotoxine for instance. In addition, due to their potent anti--cholinesterase activity, these compounds could be useful against Alzheimer's disease.

The invention further provides a process for the preparation of the compounds according to the invention, which process comprises reacting a compound of the general formula II



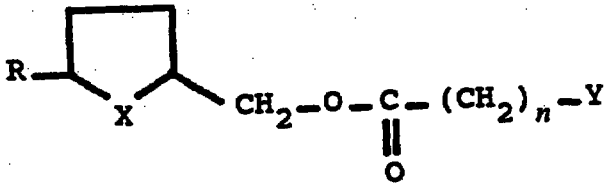
II

wherein R and X are as above defined with a compound of the general formula III



III

wherein n is as above defined and Y represents a halogen atom, and treating the resultant compound of the general formula IV



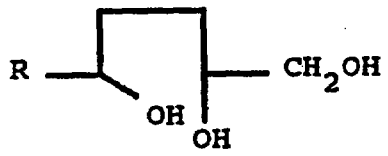
IV

wherein X, n, R and Y are as above defined with pyridine; and, if in the desired derivative $Z^{\ominus}$ is not a halogen anion, then converting the resultant halide to the desired salt.

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The reaction of the compounds II and III is suitably carried out in an inert solvent such as dry chloroform at room temperature in the presence of triisopropylbenzene-sulphonyl chloride and pyridine.

The compounds of the general formula II may be prepared in a multi-step process leading to a triol of the general formula V



V

wherein R is as above defined. This triol V may be cyclised to form the tetrahydrofuran or tetrahydrothiophen ring using protecting groups, mesylation and respectively H_2O or Na_2S treatment.

The invention is illustrated by the following Examples.

EXAMPLE 1

2-tridecyl-5-(5-pyridiniumpentanoyloxymethyl)-tetrahydrofuran chloride

X = O, n = 4, R = $CH_3(CH_2)_{12}$, $Z^{\ominus}$ = $Cl^{\ominus}$

Step a: Preparation of 2-tridecyl-5-(5-chloropentanoyloxymethyl)-tetrahydrofuran.

A mixture of 2 g (7 mmoles of 2-tridecyl-5-hydroxymethyl tetrahydrofuran, 1.43 g (10.5 mmoles) of 5-chloropentanoic acid and 4.24 g (14 mmoles) of triisopropylbenzenesulphonyl chloride in dry chloroform (20 ml) and pyridine (10 ml) was stirred at room temperature for 24 hours.

The reaction was quenched by adding 50 ml of water. The solution was made alkaline by addition of sodium bicarbonate. The aqueous layer was then extracted with chloroform. After washing successively with water, 1N sulphuric acid, water, aqueous sodium carbonate solution and water, the organic layer was dried over anhydrous

magnesium sulphate and concentrated in vacuo. The residue was then chromatographed on a silica gel column using 5% and 10% diethyl ether in petroleum ether to yield 1.42 g of the title compound as an oil.

IR (film) 2950, 2880 (C-H), 1750 (C=O), 1190, 1110 (C-O) cm^{-1}. ^{1}HNMR (80 MHz, $CDCl_3$), HMDS), δ 4.02 (m, 4H, CH_2OCO + CH-O), 3.55 (t, 2H, CH_2Cl), 2.35 (t, 2H, CH_2CO), 2.22-1.37 (m, 10H, CH_2-C-O-, CH-C-CO + CH_2-C-Cl), 1.22 (large s, 22H, $(CH_2)_{11}$), 0.81 (t, 3H, CH_3).

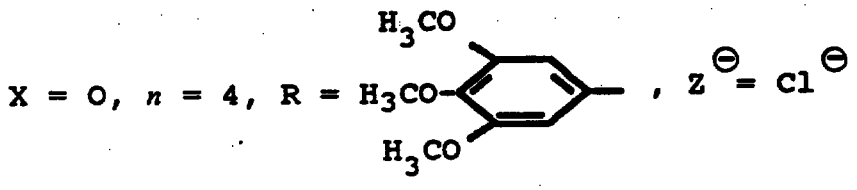
Step b: Preparation of 2-tridecyl-5-(5-pyridinium pentanoyloxymethyl)-tetrahydrofuran chloride.

0.5 g (1.24 mmoles) of the compound prepared in step (a) were refluxed overnight in 5 ml of dry pyridine. After concentration in vacuo, the brown residue was purified on a silica gel column using successively 1, 2, 5 and 10% methanol in chloroform leading to 0.4 g of the title compound as a hygroscopic waxy compound.

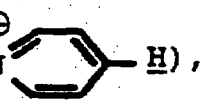
IR (film) 3060 (aromatic C-H), 2860, 2950 (C-H), 1740 C=O), 1640 (C=N), 1590 (C=C), 1180, 1100 (C-O) cm^{-1}, ^{1}HNMR (80 MHz, $CDCl_3$, HMDS) δ 9.71 (d, 2H, CH=$\overset{\oplus}{N}$), 8.65 (t, 1H, ), 8.25 (t, 2H, 2CH = C-$\overset{\oplus}{N}$), 5.12 (t, 2H, $CH_2\overset{\oplus}{N}$), 3.97 (m, 4H, CH_2-OCO + 2CH-O), 2.42 (t, 2H, CH_2CO), 2.27-1.42 (m, 10H, CH_2-C-O, CH_2-C-CO + CH_2-C-$\overset{\oplus}{N}$), 1.22 (large s, 22H, $(CH_2)_{11}$), 0.82 (t,3H, CH_3).

EXAMPLE 2

2-(3,4,5-trimethoxyphenyl)-5-(5-pyridiniumpentanoyloxy-methyl)-tetrahydrofuran chloride

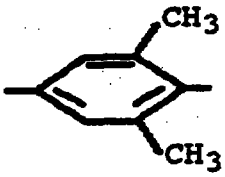


Using 2-(3,4,5-trimethoxyphenyl)-5-hydroxymethyl-tetrahydrofuran instead of 2-tridecyl-5-hydroxymethyl-tetrahydrofuran in the process described in Example 1, the title compound was obtained as a very hygroscopic compound.

IR (KBR) 3060 (aromatic, C-H), 2920 (C-H), 1735 (C=O), 1635 (C=N), 1595 (C=C), 1180, 1130, 1035 (C-O) cm^{-1}. ^{1}HNMR (80 MHz, $CDCl_3$, HMDS) δ :9.71 (d, 2H, $CH=\overset{\oplus}{N}$), 8.48 (t, 1H, ), 8.08 (t, 2H, $CH=C-\overset{\oplus}{N}$), 6.62 (s, 2H, aromatic H), 5.52-4.77 (m, 3H, $CH_2\overset{\oplus}{N}$ + ϕ-C<u>H</u>-O), 4.42 (m, 1H, CH-O), 4.17 (t, 2H, CH_2OCO), 3.87 (s, 9H, CH_3O), 2.63-1.55 (m, 10H, CH_2CO + CH_2-C-CO + $CH_2-C-\overset{\oplus}{N}$ + CH_2-C-O).

EXAMPLE 3

2-(2,4,6-trimethylphenyl)-5-(5-pyridiniumpentanoyloxy-methyl)-tetrahydrofuran chloride

X = O, n = 4, R = , $Z^{\ominus} = Cl^{\ominus}$

Following the procedure described in Example 1, but using 2-(2,4,6-trimethylphenyl)-5-hydroxymethyl-tetrahydrofuran instead of 2-tridecyl-5-hydroxymethyl-tetrahydrofuran, the title compound was obtained as a very hygroscopic compound.

^{1}HNMR (80MHz, $CDCl_3$) HMDS) δ 9.28 (d,2H, $CH=\overset{\oplus}{N}$), 8.42 (m, 1H, ), 7.98(m, 2H, $CH=C-\overset{\oplus}{N}$), 6.75 (s, 2H, aromatic H), 5.25 (m, 1H, ϕ-C<u>H</u>-O), 4.90 (m, 2H, $CH_2\overset{\oplus}{N}$), 4.60 - 3.96 (m, 3H, CH_2OCO + CH-O), 2.57-1.37(m, 10H, CH_2-CO + CH_2-C-O + $CH_2-C-\overset{\oplus}{N}$), 2.27 (s, 6H, ortho-$CH_3$), 2.17(s, 3H, para-$CH_3$).

EXAMPLE 4

2-tridecyl-5-(5-pyridiniumpentanoyloxymethyl)-tetrahydrothiophen chloride

X = S, n = 4, R = $CH_3(CH_2)_{12}$, $Z^{\ominus}$ = $Cl^{\ominus}$

Operating as described in Example 1, but using 2-tridecyl--5-hydroxymethyl-tetrahydrothiophen instead of 2-tridecyl--5-hydroxymethyl-tetrahydrofuran, the title compound was obtained as a highly hygroscopic compound.

^{1}HNMR (80MHz, $CDCl_3$, HMDS) δ 9.35 (d, 2H, $CH{=}\overset{\oplus}{N}$), 8.56 (t, 1H, ), 8.15 (m, 2H, $CH{=}C{-}\overset{\oplus}{N}$), 4.97 (m, 2H, $CH_2\overset{\oplus}{N}$), 3.45 (m, 2H, CH-S), 2.37 (t, 2H, CH_2CO), 2.22 - 1.4 (m, 12H, $CH_2{-}C{-}\overset{\oplus}{N}$ + $CH_2{-}C{-}CO$ + $CH_2{-}C{-}S$), 1.2 (large s, 22H, $(CH_2)_{11}$), 0.82 (t, 3H, CH_3).

TOXICOLOGY

The compounds of theinvention 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 on New Zealand rabbits

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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 dimethylsulphoxide

(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).

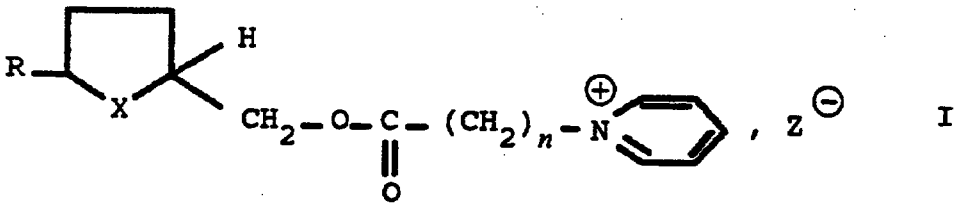
This method was described in detail in LABORATORY INVESTIGATIONS, Vol. 41, No. 3, p. 275, 1979, JEAN-PIERRE CAZENAVE, Dr. MED., JACQUES BENVENISTE, Dr. MED., AND J. FRASER MUSTARD, M.D., "Aggregation of Rabbits Platelets by Platelet-Activating Factor is independent of the Release Reaction and the Arachidonate 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 : 3.04 $.10^{-6}$
compound of Example 2 : 3.7 $.10^{-5}$
compound of Example 3 : 3.86 $.10^{-6}$
compound of Example 4 : 1.7 $.10^{-5}$.

CLAIMS:

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



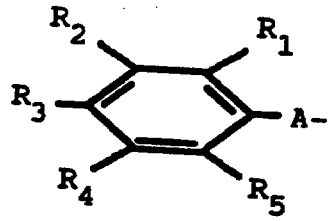
I

wherein

X represents an oxygen or sulphur atom,

n is an integer of from 1 to 6,

R represents a straight chain or branched chain alkyl group having from 1 to 13 carbon atoms, a cycloalkyl group having from 5 to 10 carbon atoms, or a group of the formula



wherein each of R_1, R_2, R_3, R_4 and R_5 independently represents a hydrogen atom or a methyl or methoxy group and A represents a valence bond or an alkyl group having from 1 to 5 carbon atoms, and

$Z^{\ominus}$ represents a pharmaceutically acceptable anion.

2. 2-Tridecyl-5-(5-pyridiniumpentanoyloxymethyl)--tetrahydrofuran chloride.

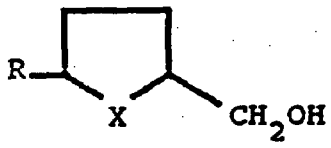
3. 2-(3,4,5-Trimethoxyphenyl)-5-(5-pyridiniumpentanoyloxymethyl)-tetrahydrofuran chloride.

4. 2-(2,4,6-Trimethylphenyl)-5-(5-pyridiniumpentanoyloxymethyl)-tetrahydrofuran chloride.

* C L M S *

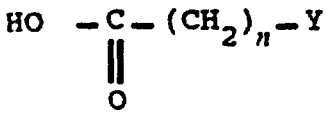
5. 2-Tridecyl-5-(5-pyridiniumpentanoyloxymethyl)--tetrahydrothiophen chloride.

6. A process for the preparation of a derivative according to claim 1, the process comprising reacting a compound of the general formula II



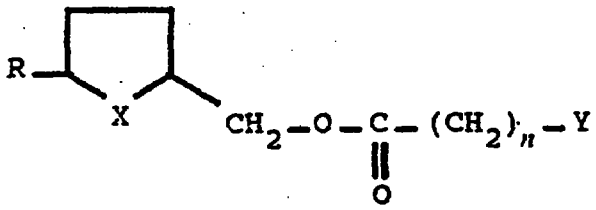
II

wherein R and X are as defined in claim 1 with a compound of the general formula III



III

wherein n is as defined in claim 1 and Y represents a halogen atom, and treating the resultant compound of the general formula IV



IV

wherein X, n, R and Y are as defined in claim 1 with pyridine; and, if in the desired derivative $Z^{\ominus}$ is not a halogen anion, then converting the resultant halide to the desired salt.

7. A process according to claim 6 in which the reaction of compounds II and III is carried out in dry chloroform at room temperature in the presence of triisopropylbenzenesulphonyl chloride and pyridine.

* C L M S *

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

