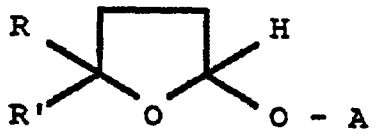
TITLE:

Tetrahydrofuran Derivatives

DESCRIPTION:

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

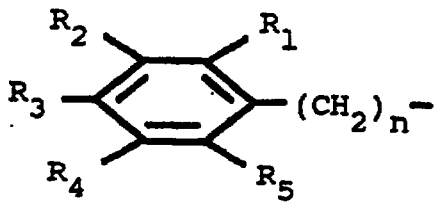
The invention provides tetrahydrofuran derivatives having the general formula I



I

wherein

either each of R and R' independently represents a hydrogen atom, a straight chain or branched chain alkyl, alkenyl or alkynyl group having from 4 to 22 carbon atoms, a cycloalkyl or cycloalkenyl group having from 5 to 10 carbon atoms, a heterocyclic ring having 5 or 6 ring atoms of which one is a nitrogen, oxygen or sulphur atom, or a group of the general formula

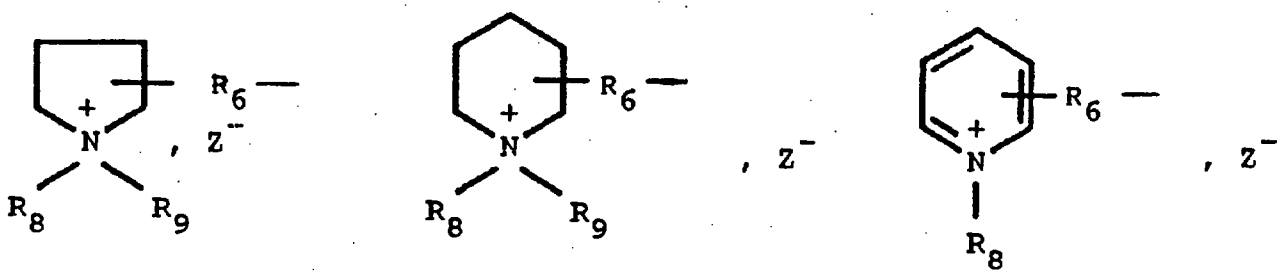


in which n is zero or an integer of from 1 to 5 and each of R_1, R_2, R_3, R_4 and R_5 independently represents a hydrogen, chlorine, bromine or iodine atom, a nitro, methoxy, trifluoromethyl, trifluoromethoxy or trifluoromethylthio group,

or R and R' together form a cycloalkyl group having from 5 to 10 carbon atoms,

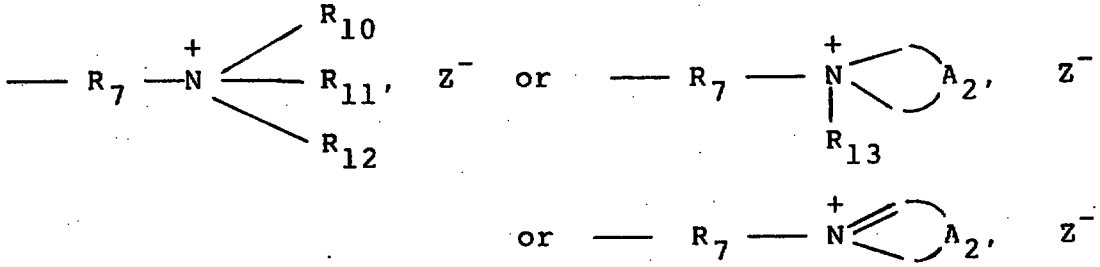
and A represents

(i) a group of the general formula



in which R_6 represents a valence bond or a saturated acyclic hydrocarbon group having up to 10 carbon atoms, each of R_8 and R_9 independently represents a hydrogen atom, a straight chain or branched chain alkyl or alkenyl group having up to 10 carbon atoms, a phenyl group or a phenylalkyl group in which the alkyl group has from 1 to 5 carbon atoms, and Z^- represents a pharmaceutically acceptable anion, or

(ii) a group of the general formula



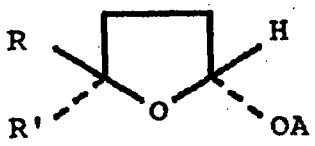
in which R_7 represents a group of the general formula $-(CH_2)_q-$ or $-(CH_2)_m-\underset{\underset{OY}{|}}{CH}-(CH_2)_p-$

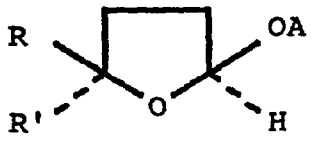
wherein q is an integer of from 2 to 11, each of m and p is an integer and m+p is not greater than 10, Y represents an alkyl or benzyl group, Z^- is as above defined, each of R_{10}, R_{11}, R_{12} and R_{13} independently represents a methyl or ethyl group and the ring NA_2 is either an optionally substituted monocyclic ring containing from 5 to 8 ring atoms of which one is the nitrogen atom shown, another is a nitrogen, sulphur, oxygen or carbon atoms, and the remainder are carbon atoms, or a bicyclic ring

containing 9 or 10 ring atoms of which one is the nitrogen atom shown, another is a nitrogen or carbon atom, and the remainder are carbon atoms, or

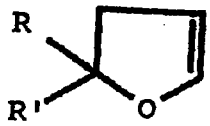
(iii) a residue obtained by removal of a hydroxy group from a hydroxy-aminoacid, from a short peptide (2 or 3 aminoacids of which at least one is a hydroxy-aminoacid) or from an ester of such a hydroxy-aminoacid or short peptide.

The invention includes both the non separated mixtures of various possible diastereoisomers and enantiomers and also each separated diastereoisomer and enantiomer.





The invention further provides a process for the preparation of tetrahydrofuran derivatives having the general formula I as above defined, the process comprising reacting a compound of the general formula II

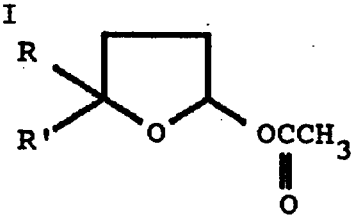


II

wherein R and R' are as above defined with an excess of up to 10% of a compound of the general formula HOB wherein B is the precursor of A containing a tertiary nitrogen atom or a halogen atom. The reaction is suitably carried out in an aprotic solvent (such as carbon tetrachloride, dimethyl-formamide or dimethylsulphoxide) at room temperature and in the presence of p-toluenesulphonic acid. Further

conversion from B to A is achieved by quaternizing the reaction product when B contains a tertiary nitrogen atom, or by treating the reaction product with a compound containing a tertiary nitrogen atom when B contains a halogen atom.

The starting material of the general formula II may be prepared by pyrolysis of the corresponding acetate of the general formula III



III

at a temperature of 200°C under reduced pressure.

The invention also provides a pharmaceutical composition comprising a tetrahydrofuran derivative as above defined in admixture with a pharmaceutically acceptable diluent or carrier.

Example 1

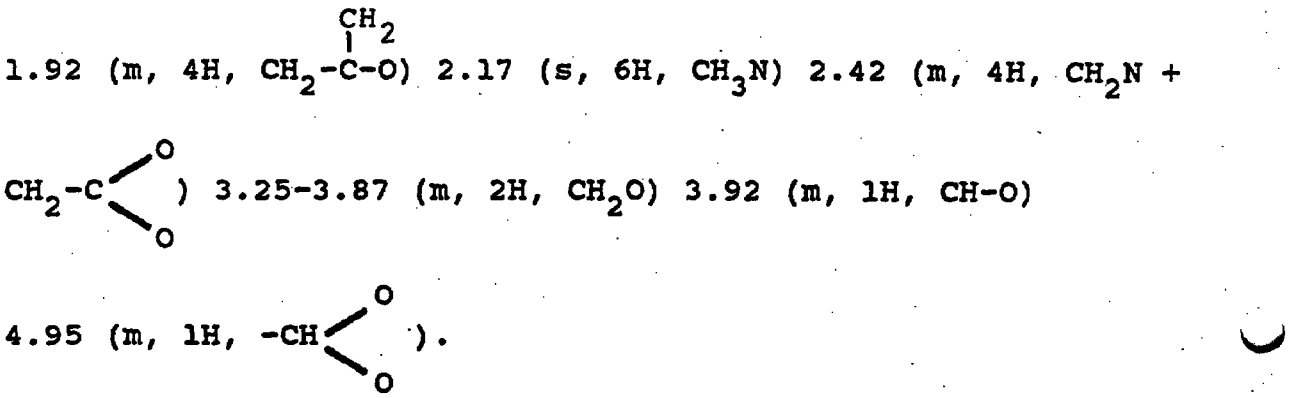
2-(2-tridecyl-tetrahydrofuran-5-yloxy)-ethyl trimethyl-ammonium iodide

$R = CH_3(CH_2)_{12}$, $R' = H$, $A = (CH_2)_2\overset{+}{N}(CH_3)_3$, I^-

Step a: Preparation of 2-tridecyl-5-dimethylaminoethoxy-tetrahydrofuran : $A = (CH_2)_2N(CH_3)_2$

A solution of 0.2 g (2.2 mmol) of dimethylamino-ethanol and 0.4 g (2.3 mmol) of dry p-toluenesulphonic acid in 50 ml of dry carbon tetrachloride was stirred at room temperature until

all the amino-alcohol had been converted into its ammonium tosylate salt as determined by thin layer chromatography (chloroform:methanol 80:20 by volume). Then 0.5 g (2 mmol) of 2-tridecyl-2,3-dihydrofuran was added and the mixture was stirred in the same conditions until complete reaction of the dihydro compound as determined by TLC (petroleum ether:ether 90:10 by volume). After evacuation of the solvent under reduced pressure, the residue was diluted by 20 ml of a saturated aqueous sodium carbonate solution and extracted several times with diethyl ether. The diethyl ether phase was washed with water until neutrality, dried on anhydrous magnesium sulphate and filtered. The residue, after evaporation of water, was chromatographed on silica gel using successively mixtures of methanol:chloroform, from 1:99 to 20:80 by volume, to yield 0.5 g of the cis-trans title compound as an oil. NMR (80MH_z, $CDCl_3$, HMDS*) δ 0.82 (t, 3H, CH_3 alkyl chain) 1.17 (large s, 22H, $(CH_2)_{11}$)



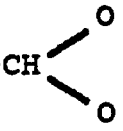
1.92 (m, 4H, CH_2-C(-CH_2)-O) 2.17 (s, 6H, CH_3N) 2.42 (m, 4H, CH_2N + CH_2-C(=O)-O) 3.25-3.87 (m, 2H, CH_2O) 3.92 (m, 1H, CH-O) 4.95 (m, 1H, -CH(-O)-O).

Step b : Preparation of 2-(2-tridecyl-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium iodide

0.2 g (0.6 mmol) of the compound prepared in step (a) above and an excess of methyl iodide (0.85 g, 6 mmol) in 50 ml of dry acetone were stirred for two hours at room temperature. After evacuation of the solvent and of the excess of methyl iodide, the residue was chromatographed on a silica gel column using a mixture of methanol:chloroform (from 5 % to 20 % by

volume of methanol) as eluent. After evaporation of the eluent, the title compound was obtained as a white solid melting at 93-94°C.NMR (80 MH_z, $CDCl_3$, HMDS*) δ 0.80 (t, 3H, CH_3 alkyl chain) 1.20 (large s, 22H, $(CH_2)_{11}$) 1.35-2.05 (m, 6H, CH_2-C-O)

3.4 (s, 9H, $CH_3\overset{+}{N}$) 3.82 (m, 5H, $CH_2\overset{+}{N}$ + CH_2-O + CH-O)

4.95 (m, 1H, ).

* HMDS means hexamethyl disiloxane and was used as standard.

Example 2

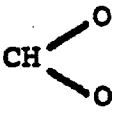
2-(2-isobutyl-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium iodide

R = $(CH_3)_2CH-CH_2$, R' = H, A = $(CH_2)_2\overset{+}{N}(CH_3)_3$, I^-

The title compound was obtained as described in Example 1 but starting with 2-isobutyl-2,3-dihydrofuran instead of 2-tridecyl-2,3-dihydrofuran. The product was a waxy solid. NMR (80 MH_z, $CDCl_3$, HMDS) δ 0.85 (d, 6H, CH_3)

1.12-2.15 (m, 7H, CH_2-C-O+ CH) 3.37 (s, 9H, $CH_3\overset{+}{N}$)

3.6-4.15 (m, 5H, CH_2O + $CH_2\overset{+}{N}$ + CH-O)

4.97 (m, 1H, ).

Example 3

2-(2-heptyl-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium iodide

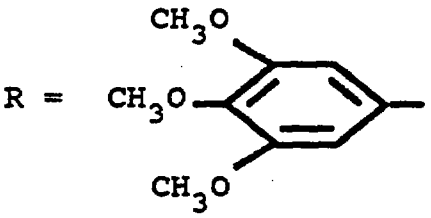
R = $CH_3(CH_2)_6$, R' = H, A = $(CH_2)_2\overset{+}{N}(CH_3)_3$, I^-

The title compound was obtained as described in Example 1 but starting with 2-heptyl-2,3-dihydrofuran instead of 2-tridecyl-2,3-dihydrofuran. The product was a low melting point compound. NMR (80 MH_z, $CDCl_3$, HMDS) δ 0.80 (t, 3H, CH_3 alkyl chain) 1.20 (large s, 10 H, $(CH_2)_5$) 1.37-2.20 (m,6H, CH_2-C-O) 3.37 (s, 9H, $CH_3\overset{+}{N}$)

3.6-4.25 (m, 5H, CH_2O + $CH_2\overset{+}{N}$ + CH-O) 4.97 (m, 1H, -CH<O,O>).

Example 4

2-[2-(3,4,5-trimethoxyphenyl)-tetrahydrofuran-5-yloxy]-ethyl trimethylammonium iodide



R = , R' = H, A = $(CH_2)_2\overset{+}{N}(CH_3)_3$, I^-

The title compound was obtained as described in Example 1 but starting with 2- (3,4,5 - trimethoxyphenyl) -2,3-dihydrofuran instead of 2-tridecyl-2,3-dihydrofuran. The product was a highly hygroscopic compound. NMR (80 MH_z, $CDCl_3$, HMDS) δ 2.00 (m, 4H, CH_2-C-O) 3.07-3,45 (m, 11H, $CH_3\overset{+}{N}$ + $CH_2\overset{+}{N}$)

3.5-3.82 (m, 11H, CH_3-O + CH_2O) 4.85 (t, 1H, CH<O,Ar>)

5.15 (m, 1H, CH<O,O>) 6.35 (m, 2H, ArH).

(Ar means aromatic ring).

Example 5

2-(cyclohexanespiro-2-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium iodide

R + R' =  , A = $(CH_2)_2\overset{+}{N}(CH_3)_3$, I^-

The title compound was obtained as described in Example 1 but starting with 2,3-dihydro- cyclohexanespiro-2-furan instead of 2-tridecyl-2,3-dihydrofuran. The product was a wax.NMR (80 MH_z, $CDCl_3$, HMDS) δ 5.12 (m, 1H, ),

3.87 (m, 4H, OCH_2 + $CH_2\overset{+}{N}$), 3.52 (s, 9H, $CH_3\overset{+}{N}$),

2.25-1.12 (m, 14H, CH_2).

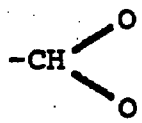
Example 6

3-(2-tridecyl-tetrahydrofuran-5-yloxy)-propyl trimethylammonium iodide

R = $CH_3(CH_2)_{12}$, R' = H, A = $(CH_2)_3\overset{+}{N}(CH_3)_3$, I^-

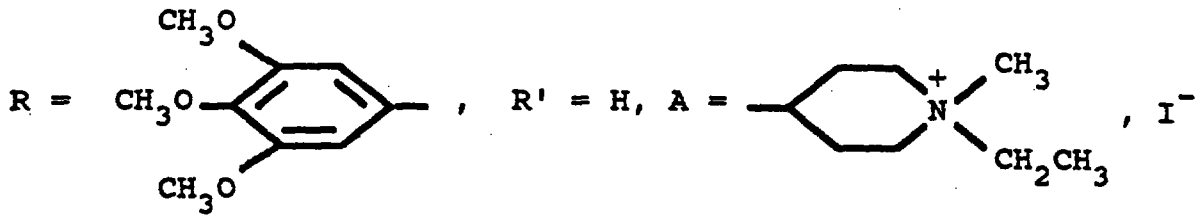
The title compound was obtained as described in Example 1 but starting with 3-dimethylamino-propanol instead of dimethylamino-ethanol. The product was a pale yellow solid melting at 81°C, NMR (80 MH_z, $CDCl_3$, HMDS) δ 0.80 (t, 3H, CH_3 alkyl chain) 1.20 (large s, 11H, $(CH_2)_{11}$) 1.35-2.20 (m, 8H,

CH_2-C-O) 3.37 (s, 9H, $CH_3\overset{+}{N}$)

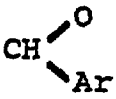
3.12-4.05 (m, 5H, CH_2O + $CH_2\overset{+}{N}$ + CH - O) 4.92 (m, 1H, ).

Example 7

4-[2-(3,4,5-trimethoxyphenyl)-tetrahydrofuran-5-yloxy] N-methyl N-ethyl-piperidinium iodide



The title compound was obtained as described in Example 1 but starting with 4-hydroxy-N-ethyl-piperidine instead of dimethylamino-ethanol. The product was a brown wax. NMR (80 MH_z, $CDLCl_3$, HMDS) δ 6.57 (m, 2H, ArH),

5.32 (m, 1H, ), 4.97 (m, 1H, ),

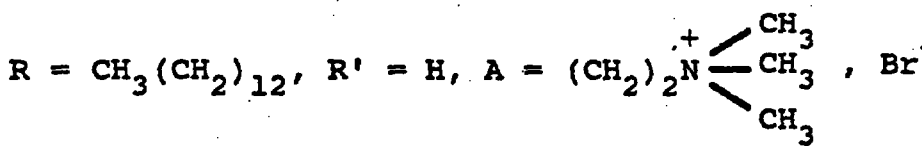
3.82 (large s, 9H, CH_3O),

3.92-3.12 (m, 10H, CH—O + $CH_2\overset{+}{N}$ + $CH_3\overset{+}{N}$),

2.35-1.61 (m, 8H, CH_2), 1.33 (t, 3H, CH_3)

Example 8

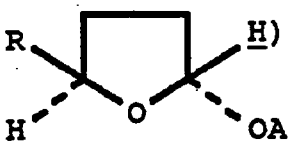
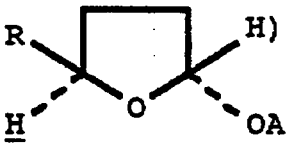
2-(2-tridecyl-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium bromide, cis and trans



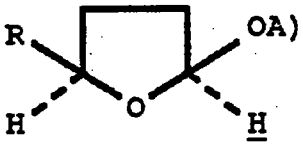
Step a : Preparation of 2-tridecyl-5-(2-bromoethoxy)-tetrahydrofuran cis and trans : A = $(CH_2)_2Br$

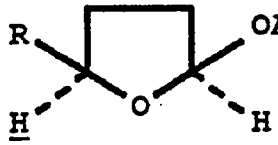
To 2 g (8 mmol) of 2-tridecyl-2,3-dihydrofuran and 1.1 g (8.8 mmol) of 2-bromo-ethanol in 50 ml of carbon tetrachloride were added 20 mg (0.1 mmol) of dry p-toluene-sulphonic acid. After stirring overnight at room temperature, the solvent was evacuated under reduced pressure. The residue was diluted with a aqueous solution of sodium carbonate and extracted with diethyl ether. The organic phase was washed with water and then dryed on anhydrous magnesium sulphate. The solvent was removed by evaporation and the residue was chromatographed on silica gel using 10 % by volume diethyl ether in petroleum ether as eluent. This method allowed

the recovery, as oils, of first the trans title compound (896 mg) then a mixture of both cis and trans isomers (419 mg) and, finally, the cis isomer (340 mg) as confirmed by their spectral data : NMR (250 MH_z, $CDCl_3$, TMS*) δ

5.16 (dd,1H, ) and 4.05 (quintet,1H, )

for the trans isomer ;

δ 5.09 (d, 1H, )

and 4.01 (quintet, 1H, ) for the cis isomer.

*TMS = tetramethyl silane used as standard.

Step b : Preparation of trans-2-(2-tridecyl-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium bromide

0.2 g (0.5 mmol) of the trans isomer prepared in step (a) above and 10 ml of a mixture of chloroform:isopropanol: dimethylformamide (3:5:5, by volume) were cooled in an ice bath and saturated with about ten times (0.3 g, 5 mmol) the theoretical amount of gaseous trimethylamine. The mixture was then stirred for two hours and gradually heated to 60-70°C. Evaporation of the solvents and of the excess of trimethylamine gave a white solid in the remaning dimethylformamide ; the solid was treated with petroleum ether and, after filtration, gave the title compound as a white powder melting at 148°C.

NMR (80 MH_z, $CDCl_3$, HMDS) δ 4.95 (m, 1H, ), 4.12-3.62 (m, 5H, CH—O + CH_2O + $CH_2\overset{+}{N}$), 3.40 (s, 9H, $(CH_3)_3\overset{+}{N}$), 2.32-1.5 (m, 6H, CH_2—C—O), 1.2 (large s, 22H, $(CH_2)_{11}$), 0.8 (t, 3H, CH_3).

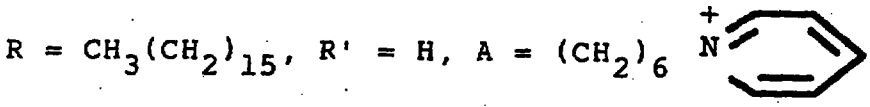
Step c : Preparation of <u>cis</u> 2-(2-tridecyl-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium bromide

This compound was obtained as described in step (b) above but starting with the <u>cis</u> isomer prepared in step (a) above. The product was a white powder melting at 154°C.

NMR (80 MH_z, $CDCl_3$, HMDS) δ 4.90 (m, 1H, ), other signals are the same as for the trans isomer.

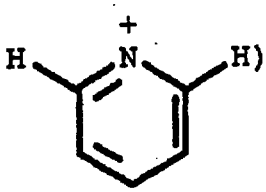
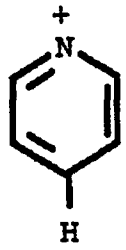
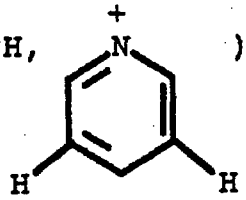
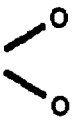
<u>Example 9</u>

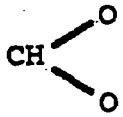
<u>6-(2-hexadecyl-tetrahydrofuran-5-yloxy)-hexyl pyridinium chloride cis and trans</u>



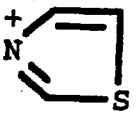
The procedure described in Example 8, step (a) was followed. However, 2-hexadecyl-2,3-dihydrofuran and 6-chlorohexanol were used instead of 2-tridecyl-2,3-dihydrofuran and 2-bromoethanol respectively, and dimethylformamide was used a solvent instead of carbon tetrachloride. This led to the forms of 2-hexadecyl-5-(6-chlorohexyloxy)-tetrahydrofuran. The substitution of the chlorine atom by pyridine was effected by heating, under stirring, overnight at 60-80°C, 0.3 g (0.7 mmol) of each of the cis and trans compounds separated with 2 ml of pyridine in 2ml of dimethylformamide. The excess pyridine and dimethyl-

formamide were evaporated off, giving residues which were chromatographed on silica gel using successively 10, 15 and 20% by volume methanol in chloroform as eluents. The title compounds were recovered as waxy solids.

<u>trans isomer</u> : NMR (80 MH_z, $CDCl_3$, HMDS) δ 9.76 (d, 2H, ), 8.63 (m, 1H, ), 8.31 (t, 2H, ), 5.16 (m, 1H, ), 4.27-3.20 (m, 5H, CH—O + CH_2O + $CH_2\overset{+}{N}$), 2.4-1.52 (m, 10H, CH_2—C—O + CH_2—C—$\overset{+}{N}$), 1.25 (large s, 32H, $(CH_2)_{14}$ + $(CH_2)_2$ in the center of the hexyl moiety, 0.83 (t, 3H, CH_3).

<u>cis isomer</u> : NMR analogous to the trans isomer except for  : δ 5.10.

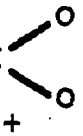
<u>Example 10</u>
<u>6-(2-hexyl-tetrahydrofuran-5-yloxy)-hexyl thiazolium chloride</u>

$R = CH_3(CH_2)_5$, $R' = H$, $A = (CH_2)_6$, Cl^-

This preparation followed that described in Example 9 but 2-hexyl-2,3-dihydrofuran was used in place of 2-hexadecyl-2,3-dihydrofuran. In the subsequent substitition reaction, thiazole was used instead of pyridine in the same conditions, and a mixture of cis and trans isomers was used rather than

each separately. The title compound was obtained as a highly hygroscopic compound.

NMR (80 MH_z, $CDCl_3$, HMDS) δ 10.53, 8.60, 8.33 (3H, thiazolium),

5.05 (m, 1H, ), 4.0 (m, 1H, CH—O), 3.6 (t, 2H, CH_2O),

3.4 (t, 2H, $CH_2\overset{+}{N}$), 2.27-1.52 (m, 10H, $CH_2-C-O + CH_2-C-\overset{+}{N}$),

1.3 (large s, 12H $(CH_2)_4 + (CH_2)_2$ of the $(CH_2)_6$ moiety),

0.81 (t, 3H, CH_3).

Example 11

3-(2-cyclopentyl-tetrahydrofuran-5-yloxy)-propyl pyridinium bromide

R = , R' = H, A = $(CH_2)_3$ , Br^-

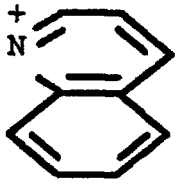
The procedure described in Example 9 was followed, but 2-cyclopentyl-2,3-dihydrofuran and 3-bromopropanol were used instead of 2-hexadecyl-2,3-dihydrofuran and 6-chlorohexanol respectively. The substitution reaction was performed on a mixture of cis and trans isomers. The title compound was obtained as a viscous oil NMR (80 MH_z, $CDCl_3$, HMDS δ 9.58, 8.65, 8.23 (5H, pyridinium),

5.08 (m, 1H, ), 4.17-3.35 (m, 5H, CH—O + CH_2O + $CH_2\overset{+}{N}$),

2.32 (m, 2H, $O-CH_2-C-\overset{+}{N}$), 2.20-1.55 (m, 7H, CH_2-C-O + CH of the cyclopentyl moiety), 1.25 (m, 8H, CH_2 of the cyclopentyl moiety).

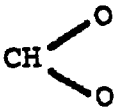
Example 12

6-[2-(p-trifluoromethylbenzyl)-tetrahydrofuran-5-yloxy]-hexyl quinolinium chloride

R = p-$CF_3C_6H_4CH_2$, R' = H, A = $(CH_2)_6$  , Cl^-

This preparation followed that described in Example 9 but 2-(p-trifluoromethylbenzyl)-2,3-dihydrofuran was used in place of 2-hexadecyl-2,3-dihydrofuran. The substitution reaction, performed on a mixture of the cis and trans isomers, used quinoline instead of pyridine. The title product was obtained as a viscous product. NMR (80 MH_z, $CDCl_3$, HMDS) δ

10.75 (1H), 9.06 (1H), 8.25 (5H) (m, quinolinium),

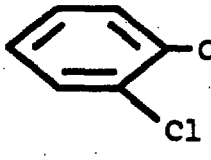
8.58 (m, 4H, C_6H_4), 5.1 (m, 1H, ),

4.2-3.1 (m, 7H, CH—O, CH_2O, $CH_2\overset{+}{N}$ and $CF_3\phi CH_2$)

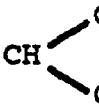
2.38-1.5 (m, 10H, $CH_2-C-\overset{+}{N}$ and CH_2-C-O), 1.25 (m, 4H, $(CH_2)_2$ of the hexyl moiety).

Example 13

2-[2-(o-chlorophenethyl)-tetrahydrofuran-5-yloxy]-ethyl trimethylammonium iodide

R = , R' = H, A = $(CH_2)_2\overset{+}{N}(CH_3)_3$, I^-

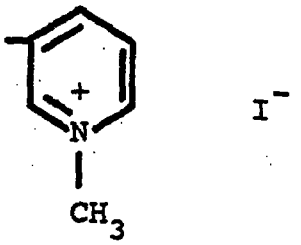
The title compound was obtained as described in Example 1, but using 2-(o-chloro-phenylethyl)-2,3-dihydrofuran instead of 2-tridecyl-2,3-dihydrofuran. The title compound was obtained as a waxy solid. NMR (80 MH_z, $CDCl_3$ HMDS) δ 7.12 (m, 4H, C_6H_4),

5.0 (m, 1H, ), 3.5-4.1 (m, 5H, CH_2O + $CH_2\overset{+}{N}$+ CH—O),

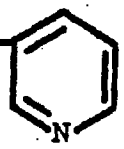
3.32 (s, 9H, $CH_3\overset{+}{N}$), 2.75 (t, 2H, ClϕCH_2),

2.20-1.10 (m, 6H, CH_2—CO).

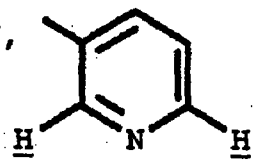
Example 14

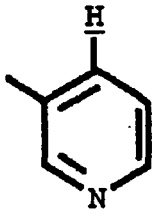
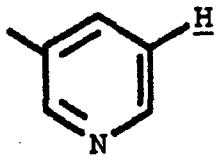
3-[(2-eicosyl-tetrahydrofuran-5-yloxy)-methyl]-pyridinium iodide R = $CH_3(CH_2)_{19}$, R' = H, A =  I^-

Step a : Preparation of 2-eicosyl-5-(pyrid-3-ylmethoxy)--tetrahydrofuran:

A = 

A solution of 0.3 g (2.8 mmol of 3-hydroxymethyl-pyridine and 0.5 g (3 mmol) of dry p-toluenesulphonic acid in 20 ml of dry dimethylsulphoxide was stirred at room temperature until all the amino alcohol had been converted into its ammonium tosylate salt, as determined by thin layer chromatography (chloroform/methanol 80:20 by volume). Then 1 g (2.8 mmol) of 2-eicosyl--2,3-dihydrofuran was added and the mixture was stirred in the same conditions until complete reaction of the dihydro compound as determined by TLC (petroleum ether/ether, 90:10 by volume). After evacuation of the solvent under reduced pressure, the residue was treated as described in Example 1 step (a) to yield 0.8 g of the cis-trans title compound as an oil.

NMR (80 MH_z, $CDCl_3$, HMDS) δ 8.67 (m, 2H, ),

7.76 (d, 1H, ), 7.35 (m, 1H, ),

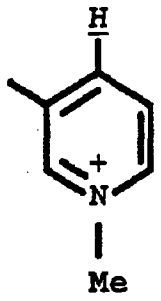
5.25 (m, 1H, CH), 4.82, 4.47 (2d, syst AB, 2H, CH_2—O),

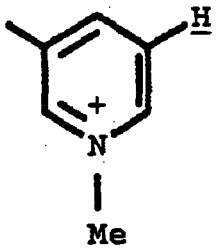
4.1 (m, 1H, CH—O), 2.25-1.5 (m, 6H, CH_2—C—O),

1.25 (large s, 36H, $(CH_2)_{18}$, 0.85 (t, 3H, CH_3).

Step b : Preparation of methyl 3-[(2-eicosyl-tetrahydrofuran-5-yloxy)-methyl]-pyridinium iodide:

The title compound was obtained as described in Example 1 step (b), starting from the compound prepared in step (a). Waxy solid. NMR (80 MH_z, $CDCl_3$, HMDS) δ

9.25 (m, 2H, H—C≡$\overset{+}{N}$), 8.5 (d, 1H, ),

8.17 (t, 1H, ), 5.26 (m, 1H, CH),

4.85 (d, 2H, OCH_2), 4.72 (s, 3H, $CH_3\overset{+}{N}$), 4.08 (m, 1H, CHO),

2.22-1.33 (m, 6H, CH_2—C—O), 1.25 (large s, 36H, $(CH_2)_{18}$),

0.85 (t, 3H, CH_3).

Example 15

N-[3-(2-hexyl-tetrahydrofuran-5-yloxy)-2-ethoxy-propyl] N-methyl piperidinium iodide

$R = CH_3-(CH_2)_5$, $R' = H$, $A = CH_2-CH(CH_3CH_2O)-CH_2$ N$^+$(CH$_3$) piperidinium

Step a : Preparation of N-[3-(2-hexyl-tetrahydrofuran-5-yloxy)--2-ethoxy-propyl]-piperidine.

$A = CH_2-CH(OEt)-CH_2$ N$^+$ piperidine

Following the procedure described in Example 14 step (a), but using 3-piperidino-2-ethoxy-propanol and 2-hexyl-2,3-dihydrofuran in place of 3-hydroxymethyl-pyridine and 2-eicosyl-2,3-dihydrofuran respectively,gave the cis-trans title compound as an oil.

NMR (80 MH_z, $CDCl_3$, HMDS) δ 5.05 (m, 1H, CH<O,O>), 3.35 (m, 2H, CH—O), 3.82-3.25 (m, 4H, CH_2O), 2.40 (m, 6H, CH_2N), 2.15-1.36 (m, 10H, CH_2-C-O + CH_2-C-N), 1.21 (large s, 10H, $(CH_2)_4$ + CH_2 piperidinyl), 1.12 (t, 3H, CH_3-C-O), 0.82 (t, 3H, CH_3).

Step b : Preparation of N-[3-(2-hexyl-tetrahydrofuran-5-yloxy)--2-ethoxy-propyl] N-methyl piperidinium iodide.

The title compound was obtained as described in Example 1 step (b), starting from the compound prepared in step (a). The title compound was recovered as a low melting point solid.

NMR (80 MH_z, $CDCl_3$, HMDS) δ 5.05 (m, 1H, ),

4.0 (m, 2H, CH—O), 3.91-3.27 (m, 10H, CH_2—O + $CH_2\overset{+}{N}$),

3.41 (s, 3H, $CH_3\overset{+}{N}$), 1.86 (m, 10H, CH_2—C—O + CH_2—C—$\overset{+}{N}$),

1.25 (large s, 10H, $(CH_2)_4$ + CH_2 piperidinyl),

1.13 (t, 3H, CH_3—C—O), 0.82 (t, 3H, CH_3).

Example 16
3-(2-hexadecyl-tetrahydrofuran-5-yloxy)-2-amino-propionic acid methyl ester

R = $CH_3(CH_2)_{15}$, R' = H, A = $CH_2\underset{\underset{NH_2}{|}}{CH}CO_2CH_3$

Operating as described in Example 1 step (a), but starting with 2-hexadecyl-2,3-dihydrofuran and serine methyl ester in place of 2-tridecyl-2,3-dihydrofuran and dimethylamino-ethanol respectively, the title compound was obtained as a hygroscopic product.

IR (film) 3380 (NH_2), 2920, 2860 (CH), 1745 (C= O), 1030 (C—O—C).

NMR (80 MH_z, $CDCl_3$, HMDS) δ 5.12 (m, 1H, ),

4.25-3.62 (m, 4H, CH—O, CH_2O + CHC(=O)), 3.8 (s, 3H, CO_2CH_3),

3.27 (m, exchangeable with D_2O, 2H, NH_2),

2.25-1.55 (m, 6H, CH_2—C—O), 1.27 (large s, 28H, $(CH_2)_{14}$,

0.85 (t, 3H, CH_3).

Example 17

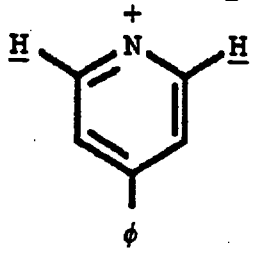
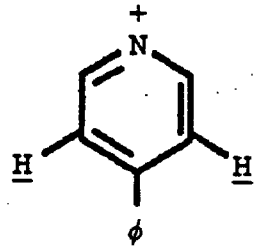
6-(2-hexyl-tetrahydrofuran-5-yloxy)-hexyl 4-phenyl-pyridinium chloride cis and trans

R = $CH_3(CH_2)_5$, R' = H, A = $(CH_2)_6$  Cl^-

Following the procedure described in Example 8 step (a), but starting from 2-hexyl-2,3-dihydrofuran and 6-chlorohexanol instead of 2-tridecyl-2,3-dihydrofuran and 2-bromoethanol respectively, there was obtained, separately, the trans and cis isomers of 2-hexyl-5-(6-chlorohexyloxy)-tetrahydrofuran.

0.45 g (1.5 mmoles) of each chloro compound, separately, was heated at 60°C to 80°C, overnight with stirring, with 1 g (7.5 mmoles) of 4-phenyl-pyridine in 2 ml of dimethylformamide. Evaporation of dimethylformamide led to residues which were chromatographed on silica gel using 10% methanol in chloroform as eluent. The title compounds were recovered as waxy solids.

<u>trans isomer</u> : NMR (80 MH_z, $CDCl_3$, HMDS) δ

9.75 (d, 2H, ), 8.30 (d, 2H, ),

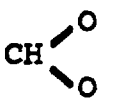
7.40 (m, 5H, C_6H_5), 5.15 (m, 1H, ),

4.25-3.20 (m, 5H, CHO + CH_2O + $CH_2\overset{+}{N}$),

2.38-1.50 (m, 10H, CH_2-C-O + $CH_2-C-\overset{+}{N}$),

1.23 (large s, 12H, $(CH_2)_4$ + $(CH_2)_2$ in the center of the hexyl moiety between O and N), 0.82 (t, 3H, CH_3).

<u>cis isomer</u> : NMR analogous to the trans isomer except for

 : δ : 5.10 ppm.

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 600 mg/kg.

PHARMACOLOGY

The pharmaceutical interest of the compounds of the invention has been established by the following experiments:

1) Inhibition of platelet aggregation on New Zealand rabbits.

The experiment was conducted on platelets in the 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 was made on a Cronolog Coultronics apparatus which determined the transmission percentage corresponding to the maximum height of the peak before the disaggregation. The percentage of variation of the inhibition with respect to the transmission percentage was 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".

2)- Action in Platelet-Activating Factor (PAF) involvement in endotoxin-induced thrombocitopenie in rabbits.

In this test the controls consisted of a batch of six rabbits administered intravenously with 1 μg/kg of PAF : this administration resulted in a reference thrombocitopenie. To determine the action of the compounds of the invention, further batches (each of 6 rabbits) were each treated with 10 mg/kg i.p. dose of the selected compound of the invention, followed 10 minutes later, by an intravenous injection of PAF as above indicated; PAF is considered as a mediator of endotoxin shock. In order to determine whether the compounds of the invention contribute to the prevention of thrombocitopenie or leukopenie in endotoxin shock, E. Coli endotoxin (0.03 mg/kg) was intravenously injected into rabbits. Pretreatment with the compounds of the invention (10 mg/kg i.p) significantly reduced the thrombocitopenie at 60 minutes (from 21 to 64%) and 180 minutes (from 16 to 68%) after the endotoxin injection.

3)- Asthma

The myotropic activities of PAF-acether, leukotriene B_4, leukotriene D_4 and histamine were compared on superfused guinea-pig parenchymal strip and were shown to have the following order of potency : PAF-acether > LTD_4 > LTB_4 > histamine. The contractile response of the lung parenchyma to PAF-acether was inhibited by aspirin and imidazole which suggested that thromboxane A_2 might play a mediator role in PAF-induced contractions. Neither an antogonist of leukotriene D_4 nor an antihistamine, mepyramine, had any effect of PAF contractions. The activity of all the compounds of the invention as antogonists of PAF was also studied on superfused lung parenchyma contracted by histamine, leukotriene B_4, leukotriene D_4 and PAF-acether.

These compounds were without effect on the histamine

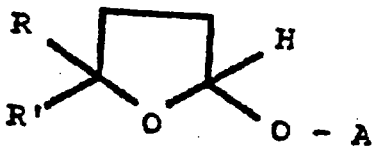
response but they slightly reduced the contractions elicited by leukotriene D_4 and potentiated those by leukotriene B_4. The compounds of the invention (7.1×10^{-6} M) inhibited by 23 - 76%, average value 63%, the contraction induced by 5.7×10^{-13} M PAF-acether and by 26 - 71%, average value 52%, that inducted by 5.7×10^{-10} M PAF-acether.

POSOLOGY

In human administration as, generally used doses are from 100 to 400 mg per diem.

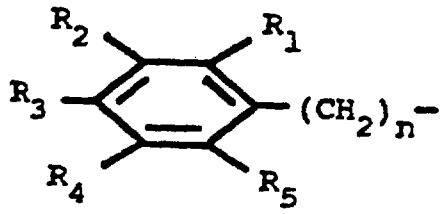
CLAIMS:

1. A tetrahydrofuran derivative having the general formula I

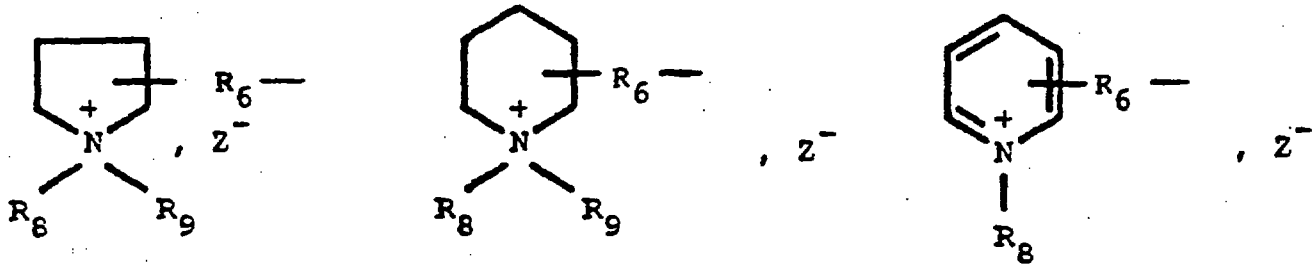


I

wherein
either each of R and R' independently represents a hydrogen atom, a straight chain or branched chain alkyl, alkenyl or alkynyl group having from 4 to 22 carbon atoms, a cycloalkyl or cycloalkenyl group having from 5 to 10 carbon atoms, a heterocyclic ring having 5 or 6 ring atoms of which one is a nitrogen, oxygen or sulphur atom, or a group of the general formula

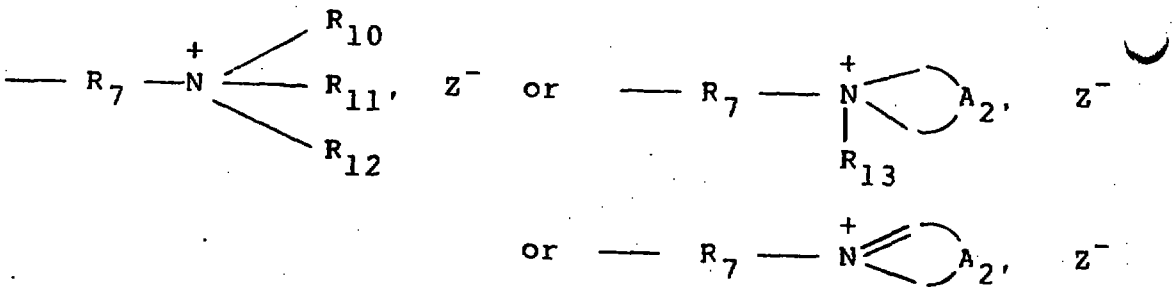


in which n is zero or an integer of from 1 to 5 and each of R_1, R_2, R_3, R_4 and R_5 independently represents a hydrogen, chlorine, bromine or iodine atom, a nitro, methoxy, trifluoromethyl, trifluoromethoxy or trifluoromethylthio group,
or R and R' together form a cycloalkyl group having from 5 to 10 carbon atoms,
and A represents
(i) a group of the general formula



in which R_6 represents a valence bond or a saturated acyclic hydrogen group having up to 10 carbon atoms, each of R_8 and R_9 independently represents a hydrogen atom, a straight chain or branched chain alkyl or alkenyl group having up to 10 carbon atoms, a phenyl group or a phenylalkyl group in which the alkyl group has from 1 to 5 carbon atoms, and Z^- represents a pharmaceutically acceptable anion, or

(ii) a group of the general formula



in which R_7 represents a group of the general formula $-CH_2)_q-$ or $-(CH_2)_m-\underset{\underset{OY}{|}}{CH}-(CH_2)_p-$ wherein q is an integer of from 2 to 11, each of m and p is an integer and m + p is not greater than 10, Y represents an alkyl or benzyl group, Z^- is as above defined, each of R_{10}, R_{11}, R_{12} and R_{13} independently represents a methyl or ethyl group and the ring NA_2 is either an optionally substituted monocyclic ring containing from 5 to 8 ring atoms of which one is the nitrogen atom shown, another is a nitrogen, sulphur, oxygen or carbon atom, and the remainder are carbon atoms, or a bicyclic ring containing 9 or 10 ring atoms of which one is the nitrogen atom shown, another is a nitrogen or carbon atom, and the remainder are carbon atoms, or

(iii) a residue obtained by removal of a hydroxy group from a hydroxy-aminoacid, from a short peptide (2 or 3 aminoacids of which at least one is a hydroxy-aminoacid) or from an ester of such a hydroxy-aminoacid or short peptide.

2. An isolated diastereoisomer or enantiomer of a tetrahydrofuran derivative according to claim 1.

3. 2-(2-Tridecyl-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium iodide.

4. 2-(2-Isobutyl-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium iodide.

5. 2-(2-Heptyl-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium iodide.

6. 2-[2-(3,4,5-Trimethoxyphenyl)-tetrahydrofuran-5--yloxy)-ethyl trimethylammonium iodide.

7. 2-(Cyclohexanespiro-2-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium iodide.

8. 3-(2-Tridecyl-tetrahydrofuran-5-yloxy)-propyl trimethylammonium iodide.

9. 4-[2-(3,4,5-Trimethoxyphenyl)-tetrahydrofuran-5--yloxy]-N-methyl-N-ethyl-piperidinium iodide.

10. 2-(2-Tridecyl-tetrahydrofuran-5-yloxy)-ethyl trimethylammonium bromide, cis and trans isomers.

11. 6-(2-Hexadecyl-tetrahydrofuran-5-yloxy)-hexyl

pyridinium chloride, cis and trans isomers.

12. 6-(2-Hexyl-tetrahydrofuran-5-yloxy)-hexyl thiazolium chloride.

13. 3-(2-Cyclopentyl-tetrahydrofuran-5-yloxy)-propyl pyridinium bromide.

14. 6-[2-(p-Trifluoromethylbenzyl)-tetrahydrofuran-5--yloxy]-hexyl quinolinium chloride.

15. 2-[2-(o-Chlorophenethyl)-tetrahydrofuran-5-yloxy]--ethyl trimethylammmonium iodide.

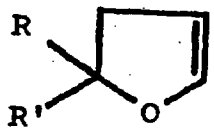
16. Methyl 3-[(2-eicosyl-tetrahydrofuran-5-yloxy)--methyl]-pyridinium iodide.

17. N-[3-(2-hexyl-tetrahydrofuran-5-yloxy)-2-ethoxy--propyl] N-methylpiperidinium oxide.

18. 3-(2-Hexadecyl-tetrahydrofuran-5-yloxy)-2-amino--propionic acid methyl ester.

19. 6-(2-Hexyl-tetrahydrofuran-5-yloxy)-hexyl 4-phenyl--pyridinium chloride, cis and trans isomers.

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



II

wherein R and R' are as defined in claim 1 with an excess of up to 10% of a compound of the general formula HOA or HOB wherein B is a precursor of A containing

* C L M S *

a secondary or tertiary nitrogen atom or a halogen atom and, if B contains a secondary or tertiary nitrogen atom, then quaternizing or salifying the reaction product, or if B contains a halogen atom, then treating the reaction product with a compound containing a secondary or tertiary nitrogen atom.

21. A process according to claim 20 in which the reaction is carried out at ambient temperature in an aprotic solvent in the presence of p-toluenesulphonic acid.

22. A process according to claim 21 in which the aprotic solvent is carbon tetrachloride, dimethylformamide or dimethylsulphoxide.

23. A pharmaceutical composition comprising a tetrahydrofuran derivative according to any of claims 1 to 19 in admixture with a pharmaceutically acceptable diluent or carrier.