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NOVEL DERIVATIVES OF THIOPYRANOPYRROLE AND PREPARATION THEREOF

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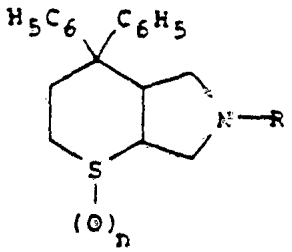
(57) Claim

1. A thiopyranopyrrole derivative

characterised in that it is of the general formula:



in which the symbol R represents a hydrogen atom, an allyl radical, a vinyloxycarbonyl radical, a tert-butoxy carbonyl radical, or a radical of the structure:

$$-CR_aR_bR_c$$

in which R_a and R_b are hydrogen atoms or phenyl radicals which are optionally substituted (by a halogen atom, an alkyl, alkoxy or nitro radical), and R_c is defined as R_a and R_b or represents an alkyl or alkoxyalkyl radical, at least one of R_a, R_b and R_c being a substituted or

.../2

unsubstituted phenyl radical, and the symbol n represents an integer from 0 to 2, it being understood that the abovementioned alkyl radicals contain 1 to 4 carbon atoms in a linear or branched chain, as well as its stereoisomeric forms and its salts when these exist.

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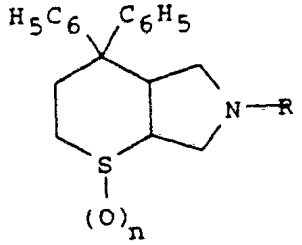


(I)

(57) Abstract

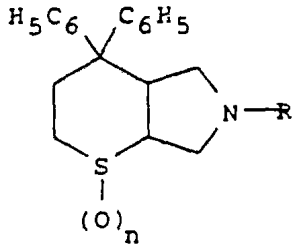
Novel derivatives of thiopyranopyrrole of general formula (I) in which R is hydrogen, allyl, or a radical having the structure: $-CR_aR_bR_c$ where R_a and R_b are hydrogen atoms or phenyl radicals optionally substituted (by halogen, alkyl, alkyloxy or nitro), and R_c is defined as R_a and R_b or stands for an alkyl or alkyloxyalkyl radical, at least one of R_a, R_b and R_c being a substituted or unsubstituted phenyl radical, and n is 0 to 2, in their stereoisomer forms, and mixtures thereof, and possibly the salts if they exist, and preparation thereof. The novel derivatives of the invention are particularly interesting as synthesis intermediates.

(57) Abrégé

Nouveaux dérivés de thiopyranopyrrole de formule générale (I) dans laquelle R est hydrogène, allyle ou un radical de structure: $-CR_aR_bR_c$ dans laquelle R_a et R_b sont des atomes d'hydrogène ou des radicaux phényle éventuellement substitués (par halogène, alcoyle, alcoyloxy ou nitro), et R_c est défini comme R_a et R_b ou représente un radical alcoyle ou alcoyloxyalcoyle, l'un au moins de R_a, R_b et R_c étant un radical phényle substitué ou non, et n = 0 à 2, sous leurs formes stéréoisomères et leurs mélanges, éventuellement leurs sels lorsqu'ils existent et leur préparation. Les nouveaux dérivés selon l'invention sont particulièrement intéressants comme intermédiaires de synthèse.

NEW THIOPYRANOPYRROLE DERIVATIVES AND THEIR PREPARATION

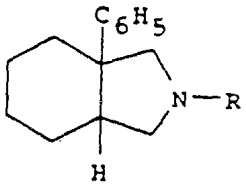
The present invention relates to new thiopyranopyrrole derivatives of general formula:



(I)

as well as their salts, when these exist, useful as intermediates in the preparation of thiopyranopyrrole derivatives, which are antagonists of the effects of substance P.

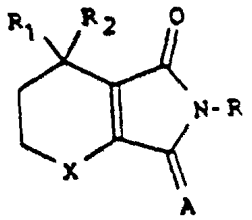
Products derived from the isoindole of general formula:



which exhibit an opium activity, have been described in American Patent 4,042,707.

These products exhibit no activity towards substance P and nor are they used in the synthesis of such products.

Herbicides of the general formula:



in which X may be a sulphur atom, R_1 and R_2 are hydrogen or alkyl and R is a substituted phenyl, have been described in European Application 0,068,822.

In spite of the research activities carried out and in spite of the interest created [M.R. Hanley, TINS, (5) 139 (1982)], practically no product has been discovered so far which acts specifically on substance P and has a nonpeptide structure, accordingly, the thiopyranopyrrole derivatives of general formula (I) are of great interest in so far as they make it possible to obtain such products.

In the general formula (I), the symbol R represents a hydrogen atom, an allyl radical, a vinyloxycarbonyl radical, a tert-butoxy carbonyl radical, or a radical of the structure:

$$-CR_aR_bR_c \qquad (Ia)$$

in which R_a and R_b are hydrogen atoms or phenyl radicals which are optionally substituted (by a halogen atom, an alkyl, alkoxy or nitro radical), and R_c is defined as R_a and R_b or represents an alkyl or alkoxyalkyl radical, at least one of R_a, R_b and R_c being a substituted or unsubstituted phenyl radical, and the symbol n represents an integer from 0 to 2.

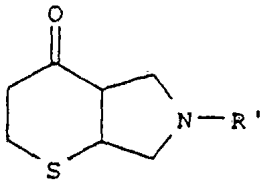
It is understood that the abovementioned alkyl radicals contain 1 to 4 carbon atoms in a linear

or branched chain.

The products of general formula (I) possess various stereoisomeric forms; it is understood that the thiopyranopyrrole derivatives of the (4aR,7aR) form or of the (4aS,7aS) form in a pure state, or in the form of a mixture of the cis- (4aRS,7aRS) forms are included within the scope of the present invention.

Furthermore, the products of general formula (I) for which n=1 also have axial or equatorial stereoisomers at the level of the S-oxide. It is understood that the position-1 R and S derivatives and mixtures thereof are also included within the scope of the present invention.

According to the invention, the thiopyranopyrrole derivative of general formula (I) may be obtained by treating the derivative of general formula:



(II)

in which R' is defined as R except for representing a hydrogen atom, successively with a phenylmagnesium halide, and then with benzene in the presence of zirconium tetrachloride, followed optionally by removal of the protective radical R' if it is desired to obtain a product for which R is a hydrogen atom, and/or followed, where appropriate, by oxidation of the

product obtained, in order to obtain a thiopyranopyrrole derivative for which n=1 or 2.

The treatment of the thiopyranopyrrole derivative of general formula (II) is carried out according to the usual methods. The treatment with a phenylmagnesium halide is advantageously carried out using phenylmagnesium bromide in an ether (for example ethyl ether), at a temperature between 20°C and the reflux temperature of the reaction mixture. The treatment with benzene in the presence of zirconium tetrachloride is carried out at a temperature of between 20°C and the reflux temperature of the reaction mixture.

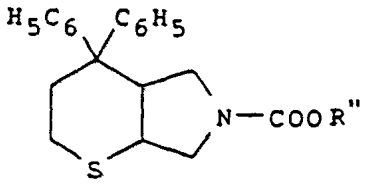
Where appropriate, when it is desired to remove the radical R', the procedure is carried out using any known method which does not affect the rest of the molecule.

In particular, when R' is other than an allyl radical, the group R' may be removed by catalytic hydrogenation in the presence of palladium. Generally, the reaction is carried out in an acidic medium in a solvent such as an alcohol (methanol, ethanol), in water or directly in acetic acid or formic acid, at a temperature between 20 and 60°C.

When R' is a benzhydryl or trityl radical, the removal may be carried out by treatment in an acidic medium, by carrying out the procedure at a temperature between 0°C and the reflux temperature of

the reaction mixture, in an alcohol, in an ether, in water or directly in acetic acid, formic acid or trifluoroacetic acid.

The group R' may also be removed by reacting vinyl chloroformate, 1-chloroethyl chloroformate or phenyl chloroformate, a product of general formula:



(III)

in which R" is a vinyl, 1-chloroethyl or phenyl radical, being obtained as an intermediate, and then by removing the radical R" by acid treatment. The reaction of the chloroformate is generally carried out in an organic solvent such as a chlorine-containing solvent (for example dichloromethane, dichloroethane, chloroform), an ether (for example tetrahydrofuran, dioxane) or a ketone (for example acetone) or in a mixture of these solvents, by carrying out the procedure at a temperature between 20°C and the reflux temperature of the reaction mixture.

The removal of the radical R" is carried out by treatment in an acidic medium for example with trifluoroacetic, formic, methanesulphonic, p-toluenesulphonic, hydrochloric or hydrobromic acid in a solvent such as an alcohol, an ether, an ester, a nitrile or a mixture of these solvents or in water, at a temperature between 0°C and the reflux temperature of

the reaction mixture.

Under the conditions for removing the abovementioned R" radicals, the thiopyranopyrrole derivative of general formula (I) is obtained directly in the form of a salt of the acid used.

When it is desired to obtain a thiopyranopyrrole derivative of general formula (I) for which n equals 1 or 2, the oxidation reaction is carried out using any known method for the oxidation of sulphides to sulphoxides or to sulphones, which does not affect the rest of the molecule, using the product for which the amine functional group is protected. For example, the procedure is carried out by reaction of an organic peracid (percarboxylic or persulphonic acid, especially perbenzoic acid, 3-chloroperbenzoic acid, 4-nitroperbenzoic acid, peracetic acid, pertrifluoroacetic acid, performic acid, permaleic acid, monoperphthalic acid, percamphoric or pertoluenesulphonic acid) or inorganic peracids (for example periodic or persulphuric acid). The reaction is advantageously carried out in a chlorine-containing solvent (methylene chloride) at a temperature between 0 and 25°C. It is also possible to carry out the procedure using tert-butylhydroperoxide in the presence of titanium tetraisopropylate.

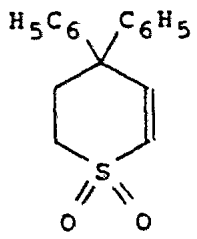
When it is desired to obtain a product of general formula (I) for which n=2, the procedure is carried out using 2 equivalents of oxidising agent.

When appropriate, the choice, the introduction and the removal of the amino-protecting radical is carried out according to the usual methods which do not affect the rest of the molecule; in particular, the procedure is carried out according to the methods described by T.W. Greene, Protective Groups in Organic Synthesis, A. Wiley - Interscience Publication (1981), or by Mc Omie, Protective Groups in Organic Chemistry, Plenum Press (1973).

It is also advantageous to carry out the procedure using the product of general formula (I) for which n=0 in the form of a salt with an inorganic acid (for example hydrochloride, sulphate).

In practice, it is understood that in order to prepare a product of general formula (I) for which n=1 or 2 and for which R is a hydrogen atom, it is advantageous to carry out the oxidation before the removal of the protective radical R'.

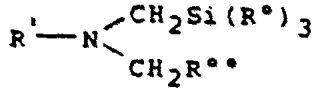
According to the invention, the thiopyranopyrrole derivative of general formula (I) for which n=2, may also be obtained from 3,4-dihydro-4,4-diphenyl-2H-thiapyran 1,1-dioxide of formula:



(IV)

by cycloaddition reaction with a silylated derivative

of general formula:

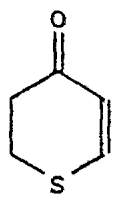


(V)

in which R' is defined as above, $(R^{\cdot})_3$ represents alkyl radicals or alkyl and phenyl radicals and $R^{\cdot\cdot}$ represents an alkoxy, cyano or phenylthio radical, followed optionally by the removal of the protective radical R' under the conditions described above if it is desired to obtain a derivative of general formula (I) for which R is a hydrogen atom.

The cycloaddition reaction is carried out in the presence of a catalytic amount of an acid chosen from trifluoroacetic acid, acetic acid, methanesulphonic acid or the acids given in the references mentioned below, in an organic solvent such as a chlorine-containing solvent (for example dichloromethane, dichloroethane), in an aromatic hydrocarbon, in a nitrile (acetonitrile) or in an ether, at a temperature between 0°C and the reflux temperature of the reaction mixture.

The thiopyranopyrrole derivative of general formula (II) may be obtained by cycloaddition reaction, by reaction of a silylated derivative of general formula (V) with 4-dehydrothiapyranone of formula:



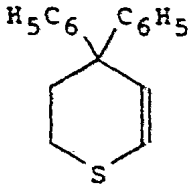
(VI)

under conditions identical to those described above for the cycloaddition reaction of this product with the sulphone of formula (IV).

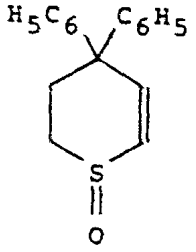
The silylated derivative of general formula (V) may be obtained according to the methods described by:

- Y. Terao et al., Chem. Pharm. Bull., 33, 2762 (1985);
- A. Hosomi et al., Chem. Lett., 1117 (1984);
- A. Padwa et al., Chem. Ber., 119, 813 (1986) or
- Tetrahedron, 41, 3529 (1985).

3,4-Dihydro-4,4-diphenyl-2H-thiapyran 1,1-dioxide of formula (IV) may be obtained by successive oxidation of 3,4-dihydro-4,4-diphenyl-2H-thiapyran and of 3,4-dihydro-4,4-diphenyl-2H-thiapyran 1-oxide of formulae:



(VII)



(VIII)

The oxidation reaction is carried out under the conditions described above for the preparation of the products of general formula (I). It is not essential to isolate the S-oxide of general formula (VIII) in order to oxidise it to a sulphone.

3,4-Dihydro-4,4-diphenyl-2H-thiapyran of general formula (VII) may be prepared according to or by analogy with the method described in Example 5

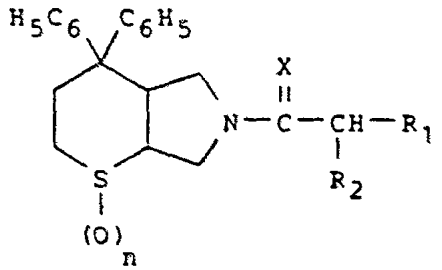
below.

It is understood that the thiopyranopyrrole derivatives of general formula (I), (II) and (III) have a number of stereoisomeric forms. The separation of the (4aR, 7aR) or (4aS, 7aS) stereoisomers is advantageously carried out with respect to the derivative of general formula (I).

The separation of the stereoisomers is carried out according to any known method which is compatible with the molecule. By way of example, the separation may be carried out by the preparation of an optically active salt, by reaction of L(+)- or D(-)-mandelic acid or of dibenzoyl tartaric acid followed by separation of the isomers by crystallisation. The desired isomer is released from its salt in a basic medium.

The separation of the axial and equatorial isomers may be carried out by chromatography or crystallisation.

According to the invention, the new thiopyranopyrrole derivatives of general formula (I) are useful for the preparation of the derivatives which antagonise the effects of substance P and which are of the general formula:



(IX)

in which:

- n is defined as above,
- the symbol X represents an oxygen atom or an NH radical,
- the symbol R_1 represents a phenyl radical which is optionally substituted by one or more halogen atoms or hydroxyl or alkyl radicals which may be optionally substituted (by halogen atoms or amino, alkylamino or dialkylamino radicals) alkoxy or alkylthio radicals which may be optionally substituted [by hydroxyl, amino, alkylamino or dialkylamino radicals optionally substituted (by phenyl, hydroxyl or amino radicals), or by dialkylamino radicals whose alkyl parts form with the nitrogen atom to which they are attached, a heterocycle with 5 to 6 members which may contain another heteroatom chosen from oxygen, sulphur or nitrogen, optionally substituted (by an alkyl, hydroxyl or hydroxyalkyl radical)], or which is substituted by amino, alkylamino or dialkylamino radicals whose alkyl parts may form with the nitrogen atom to which they are attached, a heterocycle such as defined above, or represents a cyclohexadienyl, naphthyl or a saturated or unsaturated, mono- or polycyclic heterocyclic radical containing 5 to 9 carbon atoms and one or more heteroatoms chosen from oxygen, nitrogen or sulphur, and
- the symbol R_2 represents a hydrogen or halogen atom or a hydroxyl, alkyl, aminoalkyl, alkylaminoalkyl,

dialkylaminoalkyl, alkoxy, alkylthio, acyloxy, carboxyl, alkoxycarbonyl, dialkylaminoalkoxycarbonyl, benzyloxycarbonyl, amino, acylamino or alkoxycarbonylamino radical,

the abovementioned alkyl or acyl radicals containing 1 to 4 carbon atoms in a linear or branched chain.

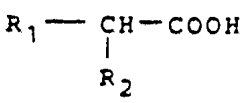
In the above general formula (IX), when R_1 contains a halogen atom, the latter may be chosen from chlorine, bromine, fluorine or iodine;

when R_1 represents a saturated or unsaturated, mono- or polycyclic heterocyclic radical, it may for example be chosen from thienyl, furyl, pyridyl, dithiinyl, indolyl, isoindolyl, thiazolyl, isothiazolyl, oxazolyl, imidazolyl, pyrrolyl, triazolyl, thiadiazolyl, quinolyl, isoquinolyl or naphthyridinyl;

when R_1 represents a phenyl which is substituted by a chain carrying a heterocycle, the latter may be chosen from pyrrolidinyl, morpholino, piperidinyl, tetrahydropyridinyl, piperazinyl or thiomorpholino;

furthermore, when the symbol R_2 is other than a hydrogen atom, the substituted chain on the thiopyranopyrrole has a chiral centre, it is understood that the stereoisomeric forms and mixtures thereof are also included within the scope of the general formula (IX).

The thiopyranopyrrole derivatives of general formula (IX) may be obtained by reaction of the acid of general formula:



(X)

or of a reactive derivative of this acid, in which R_1 and R_2 are defined as above, with a thiopyranopyrrole derivative of general formula (I) for which R is a hydrogen atom and n is defined as above, followed, where appropriate, by conversion of the amide obtained to an amidine for which X represents an NH radical.

It is understood that the amino, alkylamino or carboxyl radicals contained in R_1 and/or R_2 are preferably protected beforehand.

The protection is carried out using any compatible group whose introduction and removal does not affect the rest of the molecule. In particular, according to the above mentioned methods.

By way of example,

- the amino or alkylamino groups may be protected with the following radicals: methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl, allyloxycarbonyl, vinyloxycarbonyl, trichloroethoxycarbonyl, trichloroacetyl, trifluoroacetyl, chloroacetyl, trityl, benzhydryl, benzyl, allyl, formyl, acetyl, benzyloxycarbonyl or its substituted derivatives;
- the acidic groups may be protected with the following radicals: methyl, ethyl, t-butyl, benzyl, substituted benzyl or benzhydryl.

Furthermore, when R_2 represents a hydroxyl radical, it is preferable to protect this radical

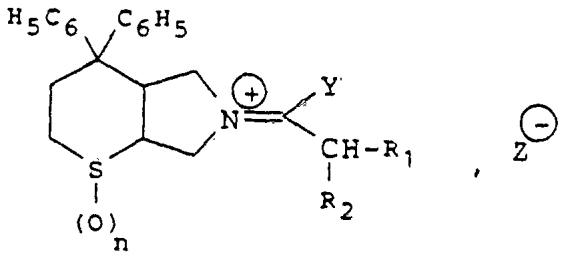
beforehand. The protection is carried out for example using an acetoxy, trialkylsilyl or benzyl radical or in the form of a carbonate using a -COORa radical in which Ra is an alkyl or benzyl radical.

When the condensation of a reactive derivative of the acid of general formula (X) is carried out, the procedure is advantageously carried out using the acid chloride, the anhydride or a mixed anhydride or a reactive ester in which the ester residue is for example a succinimido, 1-benzotriazolyl, 4-nitrophenyl, 2,4-dinitrophenyl, pentachlorophenyl or phthalimido radical or a derivative.

The reaction is generally carried out at a temperature between -40 and +40°C, in an organic solvent such as a chlorine-containing solvent (for example dichloromethane, dichloroethane, chloroform), an ether (for example tetrahydrofuran, dioxane), an ester (for example ethyl acetate), an amide (for example dimethylacetamide, dimethylformamide), or a ketone (for example acetone) or in a mixture of these solvents, in the presence of an acid acceptor such as a nitrogen-containing organic base such as for example pyridine, dimethylaminopyridine, N-methylmorpholine or a trialkylamine (especially triethylamine) or such as an epoxide (for example propylene oxide). It is also possible to carry out the procedure in the presence of a condensation agent such as a carbodiimide, [for example dicyclohexylcarbodiimide or

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide], N,N'-carbonyldiimidazole or 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline or alternatively in a dilute organic medium, in the presence of an alkaline condensation agent such as sodium bicarbonate, and where appropriate, the amide obtained is then converted to an amidine as defined above.

The conversion of the amide of general formula (IX) to an amidine for which X is an NH radical, is carried out by preparing the derivative of general formula:



(XI)

in which R_1, R_2 and n are as defined above, Y represents a chlorine atom, a methoxy or ethoxy radical and Z^- represents a chloride, tetrafluoroborate, fluorosulphonate, trifluoromethylsulphonate, methyl sulphate or ethyl sulphate ion and subsequently by reacting ammonia with the derivative of general formula (XI).

The preparation of the derivative of general formula (XI) in which Y is a chlorine atom or a methoxy or ethoxy radical is carried out by reaction of a reagent such as phosgene, phosphorus oxychloride, phosphorus pentachloride, thionyl chloride, oxalyl

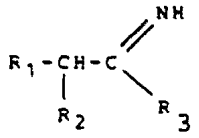
chloride, trichloromethyl chloroformate, triethyl- or trimethyloxonium tetrafluoroborate, methyl or ethyl triflate, methyl or ethyl fluorosulphonate or methyl or ethyl sulphate. The reaction is carried out in a chlorine-containing solvent (for example dichloromethane, dichloroethane) or in an aromatic hydrocarbon (for example toluene), at a temperature between 0°C and the reflux temperature of the reaction mixture. The reaction of ammonia with the derivative of general formula (XI) is carried out in an anhydrous organic solvent such as a chlorine-containing solvent (for example dichloromethane, dichloroethane), in an alcohol-chlorine-containing solvent mixture, in an ether (for example tetrahydrofuran), in an ester (for example ethyl acetate), in an aromatic solvent (for example toluene) or in a mixture of these solvents, at a temperature between -20°C and the reflux temperature of the reaction mixture.

It is not essential to isolate the derivative of general formula (XI) in order to use it in this reaction.

The acids of general formula (X) may be prepared according to the methods described in the examples below, or by analogy with these methods.

The thiopyranopyrrole derivatives of general formula (IX) for which X is an NH radical, may also be obtained from the thiopyranopyrrole derivative of general formula (I) for which R is a hydrogen atom, by

reaction of a product of general formula:



(XII)

optionally in the form of a salt, in which R_1 and R_2 are as defined above and R_3 represents an alkoxy radical containing 1 to 4 carbon atoms in a linear or branched chain, or a methylthio, ethylthio, benzylthio or alkoxycarbonylmethylthio radical.

The reaction is carried out using the derivative of general formula (XII), which is optionally prepared in situ, in an organic solvent such as a chlorine-containing solvent (for example dichloromethane, dichloroethane), an ether (for example tetrahydrofuran), an aromatic hydrocarbon (for example toluene) or a nitrile for example acetonitrile, at a temperature between 0°C and the reflux temperature of the reaction mixture.

It is understood that should the radicals R_1 and/or R_2 of the product of general formula (XII) carry substituents which may interfere with the reaction, these substituents should be protected beforehand.

The new thiopyranopyrrole derivatives of general formula (I) and the derivatives of general formula (IX) which they produce, may be purified, where appropriate, by physical methods such as crystallisation or chromatography.

Where appropriate, the new derivatives of general formula (I) or the derivatives of general formula (IX) for which the symbols R_1 and/or R_2 contain amino or alkylamino substituents and/or X represents an NH radical, may be converted to the addition salts with acids. The salts formed with inorganic acids (hydrochlorides, hydrobromides, sulphates, nitrates, phosphates) or with organic acids (succinates, fumarates, tartrates, acetates, propionates, maleates, citrates, methanesulphonates, p-toluenesulphonates, isethionates or with substituted derivatives of these compounds) may be mentioned as examples of addition salts with acids.

Substance P is known to be involved in a certain number of pathological domains:

- Agonists and Antagonists of Substance P, A.S. Dutta Drugs of the Future, 12 (8), 782 (1987);
- Substance P and Pain: an updating, J.L. Henry, TINS, 3 (4), 97 (1980);
- Substance P in Inflammatory Reactions and Pain, S. Rosell, Actual. Chim. Ther., 12th series, 249 (1985);
- Effects of Neuropeptides on Production of Inflammatory Cytokines by Human Monocytes, M. Lotz et al., Science, 241, 1218 (1988);
- Neuropeptides and the Pathogenesis of Allergy, Allergy, 42, 1 to 11 (1987);
- Substance P in Human Essential Hypertension, J. Cardiocascular Pharmacology, 10 (suppl. 12), 5172

(1987).

The thiopyranopyrrole derivatives of general formula (IX) which antagonise the effects of substance P may find an application in the domains of analgesia, inflammation, asthma, allergies, on the central nervous system, on the cardiovascular system, as an antispasmodic, or on the immune system as well as in the domain of the stimulation of lachrymal secretions.

Indeed, these products exhibit an affinity for substance P receptors at doses of between 10 and 2000 nM according to the technique described by C.M. Lee et al., Mol. Pharmacol., 23, 563-69 (1983).

Furthermore, it has been demonstrated, using various products, that it is a substance P-antagonising effect. In the technique described by S. Rosell et al., Substance P, Ed. by US Von Euler and B. Pernow, Raven Press, New York (1977), pages 83 to 88, the products studied proved to be active at doses of between 20 and 2000 nM.

Moreover, the thiopyranopyrrole derivatives according to the present invention are not toxic, they proved nontoxic in mice by the subcutaneous route at a dose of 40 mg/kg or by the oral route at a dose of 100 mg/kg.

The following products are of particular interest:

- 4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole;
- 4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1-oxide;

- 4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1,1-dioxide;
- 4,4-diphenyl-6-vinyloxycarbonylperhydrothiopyrano-[2,3-c]pyrrole;
- 4,4-diphenyl-6-tert-butyloxycarbonylperhydrothio-pyrano[2,3-c]pyrrole 1-oxide;

as well as their salts, their stereoisomeric forms and mixtures thereof.

The following examples, given with no limitation being implied, illustrate the present invention.

In the following examples, it is understood, unless specifically stated, that the proton NMR spectra were established at 250 MHz in dimethyl sulphoxide; the chemical shifts are expressed in ppm.

Example 1

4.35 g of (4aRS,7aRS)-4,4-diphenyl-6-vinyl-oxycarbonyl-perhydrothiopyrano[2,3-c]pyrrole are treated with 30 cm^3 of a 5.7 N solution of hydrochloric acid in dry dioxane for 30 minutes at 20°C. The solution is concentrated to dryness under reduced pressure (2.7 kPa), the residue is taken up in 150 cm^3 of ethanol, the resulting solution is refluxed for 30 minutes and it is then concentrated to dryness. The solid obtained is washed with 50 cm^3 of ethyl ether, drained and dried. 3.64 g of (4aRS,7aRS)-4,4-diphenyl-perhydrothiopyrano[2,3-c]pyrrole hydrochloride are obtained in the form of a white solid.

Infrared spectrum (KBr, characteristic bands cm^{-1}): 3060, 3030, 3000, 2250, 1600, 1495, 1580, 1450, 755, 710, 700.

Proton NMR spectrum (DMSO-d_6, main signals): 2.2 to 2.9 (mt, 4H, CH_2 at 2 and CH_2 at 3); 2.4 and 3.3 (2mt, 2H, CH_2 at 5); 3.08 (d, J=12.5, 1H, 1H at 7); 3.7 (mt, 1H, H at 4a); 4.16 (t, J=5, 1H, H at 7a); 7.1 to 7.5 (mt, 10H, aromatics).

(4aRS,7aRS)-4,4-Diphenyl-6-vinyloxycarbonyl-perhydrothiopyrano[2,3-c]pyrrole may be prepared in the following manner:

1.72 cm^3 of vinyl chloroformate are added to 6.2 g of (4aRS,7aRS)-6-benzyl-4,4-diphenylperhydrothiopyrano-[2,3-c]pyrrole in 50 cm^3 of 1,2-dichloroethane. The mixture is refluxed for 15 minutes and then concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (0.04 mm-0.06 mm, diameter 25 cm), eluting under a nitrogen pressure of 0.6 bar, with a cyclohexane and ethyl acetate mixture (90/10 by volume) and collecting fractions of 60 cm^3. Fractions 5 to 16 are pooled and concentrated to dryness under reduced pressure (2.7 kPa), the residue is triturated in 70 cm^3 of diisopropyl oxide, the suspension is filtered and the solid drained and dried. 4.35 g of (4aRS,7aRS)-4,4-diphenyl-6-vinyloxycarbonylperhydrothiopyrano-[2,3-c]pyrrole are obtained in the form of a white solid; melting point 160°C.

(4aRS,7aRS)-6-Benzyl-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole may be prepared in the following manner:

43.7 g of zirconium tetrachloride are added to a solution of 12.2 g of (4RS,4aSR,7aRS)-4-hydroxy-4-phenyl-6-benzylperhydrothiopyrano[2,3-c]pyrrole in 180 cm^3 of benzene. The reaction mixture is refluxed for 1 hour and then brought to 20°C and diluted with 200 cm^3 of dichloromethane. 150 cm^3 of a 4N aqueous solution of sodium hydroxide are added to the resulting cooled solution. The suspension obtained is filtered, the filtrate is decanted, the organic phase is washed with 200 cm^3 of a saturated aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The oil obtained is chromatographed on a silica gel column (0.04 mm-0.06 mm, diameter 5.2 cm, height 39 cm), eluting under a nitrogen pressure of 0.6 bar, with a cyclohexane and ethyl acetate mixture (90/10 by volume) and collecting fractions of 125 cm^3. Fractions 19 to 32 are pooled and concentrated to dryness under reduced pressure (2.7 kPa). The oil obtained is crystallised from 200 cm^3 of diisopropyl oxide, the crystals are drained and dried. 6.2 g of (4aRS,7aRS)-6-benzyl-4,4-diphenylperhydrothiopyrano-[2,3-c]pyrrole are obtained in the form of orange-coloured crystals; melting point 130°C.

(4RS,4aSR,7aRS)-4-Hydroxy-4-phenyl-6-benzyl-

perhydrothiopyrano[2,3-c]pyrrole may be prepared in the following manner:

A solution of 21.15 g of (4aRS,7aSR)-6-benzyl-4-oxoperhydrothiopyrano[2,3-c]pyrrole in 150 cm^3 of anhydrous ethyl ether are added over 30 minutes to a solution of phenylmagnesium bromide prepared from 19.8 cm^3 of bromobenzene and 4.52 g of dry magnesium in 120 cm^3 of anhydrous ethyl ether. The reaction mixture is stirred at the reflux temperature for 3 hours, and then for 20 hours at 20°C. The mixture, to which 200 cm^3 of ethyl ether has been added, is stirred with 600 cm^3 of a saturated aqueous solution of ammonium chloride. The aqueous phase is extracted with 200 cm^3 of ethyl ether, the two pooled etherial extracts are washed twice with 300 cm^3 of a saturated aqueous solution of sodium chloride and then dried over magnesium sulphate and concentrated to dryness under reduced pressure (5.4 kPa) at 35°C. 12.2 g of (4RS,4aSR,7aRS)-4-hydroxy-4-phenyl-6-benzylperhydrothiopyrano[2,3-c]pyrrole are obtained in the form of a white solid; melting point 137°C.

(4aRS,7aSR)-6-Benzyl-4-oxoperhydrothiopyrano-[2,3-c]pyrrole may be prepared in the following manner:

5 drops of trifluoroacetic acid are added to a solution of 20 g of 4-dehydrothiapyranone and 54 cm^3 of N-butoxymethyl-N-trimethylsilylmethylbenzylamine in 100 cm^3 of anhydrous dichloromethane, and the mixture is stirred for 4 hours while maintaining the temperature

at 20°C. The reaction mixture is stirred with 5 g of potassium carbonate, filtered and then concentrated to dryness under reduced pressure (2.7 kPa). The oily residue is chromatographed on a silica gel column (0.04 mm-0.06 mm, diameter 9.2 cm), eluting under a nitrogen pressure of 0.6 bar with a cyclohexane and ethyl acetate mixture (90/10 by volume) and then with the cyclohexane and ethyl acetate mixture (75/25 by volume) and collecting fractions of 250 cm^3. Fractions 35 to 56 are pooled and concentrated to dryness under reduced pressure (2.7 kPa). 24 g of (4aRS,7aSR)-6-benzyl-4-oxoperhydrothiopyrano[2,3-c]pyrrole are obtained in the form of a yellow oil.

Infrared spectrum (CCl_4 solution, characteristic bands cm^{-1}): 3090, 3070, 3025, 2925, 2850, 2800, 2730, 1710, 1600, 1585, 1495, 1475, 1450, 700.

Proton NMR spectrum ($CDCl_3$, main signals): 2.42 (dd, J=10 and 7, 1H, 1H at 7); 2.66 (mt, 2H, CH_2 at 5); 3.05 (mt, 1H, H at 4a); 3.1 (dd, J=10 and 7.5, 1H from CH_2 at 7); 3.61 (s, 2H, N-CH_2-Ar); 3.8 (dt, J=7.5 and 7, 1H, H at 7a); 7.15 to 7.35 (mt, 5H aromatics).

Example 2

3.98 g of 4,4-diphenyl-6-tert-butyloxycarbonylbutyloxycarbonylperhydrothiopyrano[2,3-c]pyrrole 1-oxide (mixture of the 1RS,4aSR,7aSR and 1RS,4aRS,7aRS isomers) are treated with 40 cm^3 of a mixture of concentrated hydrochloric acid (37% hydrochloric acid) and dioxane (1/2 by volume) for 48 hours at 20°C. The

solution is concentrated to dryness at 40°C under reduced pressure (2.7 kPa). The oil obtained is taken up in 30 cm^3 of dichloromethane, the solution is washed with 60 cm^3 of a 2N aqueous solution of sodium hydroxide, the aqueous phase is extracted with 20 cm^3 of dichloromethane. The organic extracts are pooled, dried over magnesium sulphate and concentrated to dryness at 40°C under reduced pressure (2.7 kPa). The residue is taken up in diisopropyl oxide and then concentrated to dryness at 40°C under reduced pressure (2.7 and then 0.13 kPa). 3.0 g of (1RS,4aRS,7aRS)-4,4-diphenyl-perhydrothiopyrano[2,3-c]pyrrole 1-oxide are obtained in the form of a white meringue.

Infrared spectrum (KBr, characteristic bands cm^{-1}): 3080, 3055, 3025, 2950, 2920, 2880, 2860, 1595, 1580, 1490, 1440, 1020, 760, 740, 700.

Proton NMR spectrum (DMSO-d_6 + CF_3CCOD, main signals): 2.26 (broad t, J=14, 1H, 1H at 3); 2.42 (dd, J=10 and 9, 1H, CH_2 at 5); 2.55 (broad dd, J=14 and 4, 1H, 1H at 3); 3.68 (t, J=6, 1H, H at 7a); 3.82 (d, J=14, 1H, H at 7); 3.8 to 4 (mt, 1H, CH at 4a); 4.15 (dd, J=14 and 6, 1H, H at 7); 7.1 to 7.5 (mt, 10H aromatics).

4,4-Diphenyl-6-tert-butyloxycarbonylperhydrothiopyrano[2,3-c]pyrrole 1-oxide (mixture of the 1RS,4aSR,7aSR and 1RS,4aRS,7aRS isomers) may be prepared in the following manner:

A solution of 2.3 g of 3-chloroperoxybenzoic acid (at 85%) in 20 cm^3 of dichloromethane is added to a

solution, cooled to 0°C, of 4.2 g of (4aRS,7aRS)-4,4-diphenyl-6-tert-butyloxycarbonylperhydrothiopyrano[2,3-c]pyrrole in 30 cm^3 of dry dichloromethane. After stirring for 1.5 hours at 3°C and 1.5 hours at 20°C, the reaction mixture is washed twice with 100 cm^3 of a saturated aqueous solution of sodium bicarbonate, and then with 100 cm^3 of distilled water, dried over magnesium sulphate, concentrated to dryness at 35°C under reduced pressure (2.7 kPa). The residue is crystallised from ethyl acetate, the crystals are washed with ethyl acetate and diisopropyl oxide, drained and then dried under reduced pressure (2.7 kPa). 3.98 g of 4,4-diphenyl-6-tert-butyloxycarbonylperhydrothiopyrano[2,3-c]pyrrole 1-oxide - (mixture of the 1RS,4aSR,7aSR and 1RS,4aRS,7aRS isomers) are obtained in the form of white crystals used as they are in the next reaction.

(4aRS,7aRS)-4,4-Diphenyl-6-tert-butyloxycarbonylperhydrothiopyrano[2,3-c]pyrrole may be prepared in the following manner:

2.89 g of ditert-butyl dicarbonate are added in fractions of 0.5 g to a suspension of 4.0 g of (4aRS,7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]-pyrrole hydrochloride and 1.70 cm^3 of triethylamine in 60 cm^3 of dry dichloromethane, followed by 0.15 g of 4-dimethylaminopyridine. The mixture is stirred for 20 hours at 20°C and then the reaction solution is washed twice with 100 cm^3 of an aqueous solution of

citric acid of pH 4 and with 100 cm^3 of water, dried over magnesium sulphate and concentrated to dryness at 35°C under reduced pressure (2.7 kPa). The residue is crystallised from ethyl ether, the crystals are drained and dried. 4.27 g of (4aRS,7aRS)-4,4-diphenyl-6-tert-butyloxycarbonylperhydrothiopyrano[2,3-c]pyrrole are obtained in the form of pink crystals; melting point 162°C.

(1RS,4aRS,7aRS)-4,4-Diphenylperhydrothiopyrano[2,3-c]pyrrole 1-oxide may also be prepared in the following manner:

A solution of 15.4 g of 3-chloroperoxybenzoic acid (at 85%) in 400 cm^3 of dichloromethane is added over 40 minutes to a solution, cooled to -3°C, of 25 g of (4aRS, 7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]-pyrrole in 500 cm^3 of dichloromethane and 100 cm^3 of methanol. After stirring for one hour at -3°C, the reaction mixture is washed with 200 cm^3 of a 10% aqueous solution of potassium hydrogen carbonate and again with 100 cm^3 of this same solution, then dried over magnesium sulphate and concentrated to dryness at 40°C under reduced pressure (2.7 kPa). The residue is crystallised from 50 cm^3 of ethyl acetate, the crystals are taken up in 200 cm^3 of dichloromethane, the solution obtained is washed with 75 cm^3 of a 1N aqueous solution of sodium hydroxide and then dried over magnesium sulphate and concentrated to dryness. The residue is crystallised from 30 cm^3 of ethyl acetate, the crystals are washed

with ethyl acetate, drained and dried. 13.6 g of (1RS,4aRS,7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]-pyrrole 1-oxide are obtained in the form of white crystals; melting point 174°C.

Example 3

3.5 g of (S)-mandelic acid and 90 cm^3 of a mixture of acetonitrile and water (99/1 by volume) are added to 7.15 g of (1RS,4aRS,7aRS)-4,4-diphenyl-perhydrothiopyrano[2,3-c]pyrrole 1-oxide. After stirring, the resulting solution is allowed to stand for 48 hours at room temperature. The crystals obtained are drained, washed with the acetonitrile-water mixture and then dried. The crystals are taken up in 200 cm^3 of a boiling acetonitrile-water mixture and after filtering while still hot, the solution obtained is allowed to stand for 5 hours at room temperature. The crystals are drained, washed twice with 10 cm^3 of acetonitrile and then dried. 1.5 g of (1R*,4aR*,7aR*)-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1-oxide (S)-mandelate are obtained; $[\alpha]_D^{20} = -228°$, (c = 0.44; acetic acid). The filtrate is allowed to stand for 20 hours at room temperature, the crystals obtained are drained, washed twice with 5 cm^3 of acetonitrile and then dried. 0.62 g of (1R*,4aR*,7aR*)-4,4-diphenyl-perhydrothiopyrano[2,3-c]pyrrole 1-oxide (S)-mandelate is obtained; $[\alpha]_D^{20} = -230°$, (c = 0.45; acetic acid).

40 cm^3 of dichloromethane and 7.0 cm^3 of 1N aqueous sodium hydroxide are added to 2.06 g of

(1R*,4aR*,7aR*)-4,4-diphenylperhydrothiopyrano[2,3-c]-pyrrole 1-oxide (S)-mandelate. The mixture is stirred for a few minutes after dissolution of the starting product, the organic phase is dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The residue is disintegrated in an ethyl acetate and ethyl ether mixture, the solid is washed with diisopropyl oxide and dried. 1.14 g of (1R*,4aR*,7aR*)-(-)-4,4-diphenylperhydrothiopyrano-[2,3-c]pyrrole 1-oxide are obtained in the form of a white solid; melting point 192°C. $[\alpha]_D^{20}$ = -405°, (c = 0.46; acetic acid).

Example 4

15.8 g of (S)-(+)-mandelic acid and 750 cm³ of a mixture of acetonitrile and water (99/1 by volume) are added to 32.3 g of (1RS,4aRS,7aRS)-4,4-diphenyl-perhydrothiopyrano[2,3-c]pyrrole 1-oxide, followed by 5.0 cm³ of water. After making lukewarm, the solution obtained is allowed to stand for 48 hours at room temperature. The crystalline suspension is filtered, and the filtrate, concentrated to dryness, gives a meringue which is taken up in 200 cm³ of the boiling acetonitrile-water mixture. The solution obtained is allowed to stand for about 20 hours at room temperature. The crystals are drained, washed with acetonitrile, dried and then again taken up in 200 cm³ of an acetonitrile-water mixture (98/2 by volume). The resulting solution is allowed to stand for about

20 hours at room temperature. The crystals are drained and dried. 9.4 g of (1R*,4aR*,7aR*)-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1-oxide (S)-(+)-mandelate are obtained; $[\alpha]_D^{20}$ = +337°, (c = 0.45; acetic acid).

100 cm³ of dichloromethane and 30 cm³ of 1N aqueous sodium hydroxide are added to 9.2 g of (1R*,4aR*,7aR*)-4,4-diphenylperhydrothiopyrano[2,3-c]-pyrrole 1-oxide (S)-(+)-mandelate. The mixture is stirred for 10 minutes, the organic phase is dried over magnesium sulphate, and concentrated to dryness under reduced pressure (2.7 kPa). The residue is disintegrated in an ethyl acetate and diisopropyl oxide mixture, the solid is washed with diisopropyl oxide and dried. 5.6 g of (1R*,4aR*,7aR*)-(+)-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1-oxide are obtained in the form of a white solid; melting point 198°C. $[\alpha]_D^{20}$ = +434°, (c = 0.45; acetic acid).

Example 5

0.58 g of (4aRS,7aRS)-4,4-diphenyl-6-vinyloxycarbonyl perhydrothiopyrano[2,3-c]pyrrole 1,1-dioxide is treated with 25 cm³ of a 5.7 N solution of hydrochloric acid in dry dioxane for 30 minutes while making lukewarm. The reaction solution is concentrated to dryness under reduced pressure (2.7 kPa) at 50°C. The residue is taken up in 15 cm³ of ethanol, the solution obtained is refluxed for 30 minutes and then concentrated to dryness. The solid obtained is washed with ethyl ether, drained and dried.

0.46 g of (4aRS,7aRS)-4,4-diphenylperhydrothiopyrano-[2,3-c]pyrrole 1,1-dioxide hydrochloride is obtained in the form of a white solid.

Infrared spectrum (characteristic bands cm^{-1}): 3055, 3030, 2970, 2935, 2825, 2300, 1600, 1495, 1462, 1335, 1315, 1300, 1140, 1120, 770, 760, 710, 595, 505.

Proton NMR spectrum (DMSO-d_6 + CF_3COOD, main signals): 3.84 (ab, 2H, CH_2 at 7); 4.0 (mt, 1H, H at 4a); 4.27 (mt, 1H, H at 7a); 7.1 to 7.6 (mt, 10H, aromatics).

(4aRS,7aRS)-4,4-Diphenyl-6-vinyloxycarbonyl-perhydrothiothiopyrano[2,3-c]pyrrole 1,1-dioxide may be prepared in the following manner:

0.16 cm^3 of vinyl chloroformate is added to a solution of 0.7 g of (4aRS,7aRS)-6-benzyl-4,4-diphenyl-perhydrothiopyrano[2,3-c]pyrrole 1,1-dioxide in 10 cm^3 of 1,2-dichloroethane. The mixture is refluxed for 2 hours and then concentrated to dryness under reduced pressure (2.7 kPa) at 50°C. The crystalline solid is washed with ethyl ether, drained and then dried. 0.58 g of (4aRS,7aRS)-4,4-diphenyl-6-vinyloxycarbonylperhydro-thiopyrano[2,3-c]pyrrole 1,1-dioxide is obtained in the form of white crystals.

Infrared spectrum (characteristic bands cm^{-1}): 3080, 3055, 3025, 2990, 2970, 2925, 2885, 1715, 1645, 1595, 1580, 1495, 1415, 1330, 1300, 1150, 1140, 1125, 945, 865, 755, 700, 510.

Proton NMR spectrum (DMSO-d_6 + CF_3COOD, main signals): 2.5 to 3.45 (mt, 6H, CH_2 at 5, at 2 and at 3); 3.8 to

4.2 (mt, 4H, CH_2 at 7, H at 4a and H at 7a); 4.46 and 4.72 (broad 2d, J=6 and J=14, 2x1H, CH=$\underline{CH_2}$); 7.0 (dd, J=14 and 6, 1H, O$\underline{CH}$=); 7.1 to 7.6 (mt, 10H, aromatics).

(4aRS,7aRS)-6-Benzyl-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1,1-dioxide may be prepared in the following manner:

2 drops of trifluoroacetic acid are added to a solution of 1.3 g of 3,4-dihydro-4,4-diphenyl-2H-thiapyran 1,1-dioxide and 1.75 cm^3 of N-butoxymethyl-N-trimethylsilylmethylbenzylamine in 12 cm^3 of anhydrous dichloromethane, and the mixture is stirred for 30 minutes at 30°C. 1.75 cm^3 of N-butoxymethyl-N-trimethylsilylmethylbenzylamine and 2 drops of trifluoroacetic acid are again added and the mixture is stirred for 2 hours at 35°C. This last procedure is once again repeated and after stirring for 1 hour, 1 g of potassium carbonate is added. The suspension is filtered and the filtrate concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 3.2 cm, height 35 cm), eluting under a nitrogen pressure of 0.5 bar with a cyclohexane and ethyl acetate mixture (80/20 by volume) and collecting fractions of 30 cm^3. Fractions 20 to 28 are pooled and concentrated to dryness under reduced pressure (2.7 kPa). 0.7 g of (4aRS,7aRS)-6-benzyl-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1,1-dioxide is obtained in the form of white crystals;

melting point 186°C.

3,4-Dihydro-4,4-diphenyl-2H-thiapyran 1,1-dioxide may be prepared in the following manner:

A solution of 1.12 g of 3-chloroperoxybenzoic acid (at 85%) in 25 cm^3 of dry dichloromethane is added to a solution of 1.47 g of 3,4-dihydro-4,4-diphenyl-2H-thiapyran 1-oxide in 15 cm^3 of dry dichloromethane. After stirring for 20 hours at 20°C the reaction mixture is washed with 50 cm^3 of a 10% aqueous solution of sodium thiosulphate and then with 50 cm^3 of a saturated aqueous solution of sodium hydrogen carbonate. The organic phase is dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The crystalline residue is washed with ethyl ether, drained and dried under reduced pressure (2.7 kPa). 1.3 g of 3,4-dihydro-4,4-diphenyl-2H-thiapyran 1,1-dioxide are obtained in the form of white crystals; melting point 166°C.

3,4-Dihydro-4,4-diphenyl-2H-thiapyran 1-oxide may be prepared in the following manner:

By carrying out the procedure as above, using 2.05 g of 3,4-dihydro-4,4-diphenyl-2H-thiapyran and 1.67 g of 3-chloroperoxybenzoic acid (at 85%), 1.9 g of 3,4-dihydro-4,4-diphenyl-2H-thiapyran 1-oxide are obtained in the form of a white solid; melting point 130°C.

3,4-Dihydro-4,4-diphenyl-2H-thiapyran may be prepared in the following manner:

3.95 cm^3 of acetic anhydride are added to a suspension of 2.7 g of 4,4-diphenyltetrahydrothiapyran 1-oxide in 30 cm^3 of anhydrous toluene. The mixture is refluxed for 20 hours and concentrated to dryness at 60°C under reduced pressure (2.7 kPa and then 0.13 kPa). The oily residue is crystallised from diisopropyl oxide, the crystals are drained and dried. 2.1 g of 3,4-dihydro-4,4-diphenyl-2H-thiapyran are obtained in the form of white crystals; melting point 78°C.

4,4-Diphenyltetrahydrothiapyran 1-oxide may be prepared in the following manner:

A solution of 20.3 g of 3-chloroperoxybenzoic acid (at 85%) in 300 cm^3 of dichloromethane is added over 40 minutes to a solution, cooled to 0°C, of 25.4 g of 4,4-diphenyltetrahydrothiapyran in 130 cm^3 of dichloromethane. After stirring for 2 hours at 0°C, 250 cm^3 of a 5% aqueous solution of potassium hydrogen carbonate are added to the mixture and it is then stirred for 15 minutes. The organic phase is again washed with 250 cm^3 of a solution of potassium hydrogen carbonate and it is then dried over magnesium sulphate and concentrated to dryness (after verifying the absence of peroxides) under reduced pressure (2.7 kPa). 26.9 g of 4,4-diphenyltetrahydrothiapyran 1-oxide are obtained in the form of a white solid; melting point 122°C.

4,4-Diphenyltetrahydrothiapyran may be

prepared in the following manner:

100 g of sodium sulphide nonahydrate are added to a suspension of 140.8 g of 3,3-diphenyl-1,5-bis-(methanesulphonyl-oxy)pentane in 1400 cm^3 of 1-butanol. The mixture is refluxed for 2 hours and then cooled to about 20°C, and then 1000 cm^3 of water, 500 cm^3 of ethyl acetate and 500 cm^3 of dichloromethane are added. After stirring, the organic phase is separated, washed successively with 1000 cm^3 of water, 500 cm^3 of 1N hydrochloric acid, 500 cm^3 of a saturated aqueous solution of sodium hydrogen carbonate and 1000 cm^3 of water, and then dried over magnesium sulphate and concentrated to dryness at 60°C under reduced pressure (2.7 kPa). The residue is crystallised from ethyl acetate, the crystals are washed with diisopropyl oxide, drained and dried. 76 g of 4,4-diphenyl-tetrahydrothiapyran are obtained in the form of white crystals; melting point 134°C.

3,3-Diphenyl-1,5-bis(methanesulphonyloxy)-pentane may be prepared in the following manner:

A solution of 62 cm^3 of methanesulphonyl chloride in 100 cm^3 of dichloromethane is added over 10 minutes to a solution, cooled to -20°C, of 95 g of 3,3-diphenyl-1,5-pentanediol (prepared according to P. EILBRACHT et al., Chem. Ber. 118, 825-839 (1985)) in 950 cm^3 of dichloromethane and 113 cm^3 of triethylamine. After stirring for 2 hours at 20°C, the reaction mixture is washed with twice 500 cm^3 of water, the

organic phase is dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The oily residue is crystallised from ethyl ether, the crystals are washed with ethyl ether, drained and dried. 140 g of 3,3-diphenyl-1,5-bis-(methanesulphonyloxy)pentane are obtained in the form of white crystals; melting point 99°C.

The products according to the invention may lead to the thiopyranopyrrole derivatives of general formula (IX) by carrying out the procedure as in the following examples:

Example of Use 1

1.18 g of N,N'-carbonyldiimidazole are added to a solution of 1.16 g of 2-dimethylaminophenylacetic acid in 20 cm^3 of dry dichloromethane. The mixture is stirred for 30 minutes at +5°C and then a solution of 2.0 g of (4aRS,7aRS)-4,4-diphenylperhydrothio-pyrano[2,3-c]pyrrole hydrochloride and 1.83 cm^3 of triethylamine in 20 cm^3 of dichloromethane is added. The reaction mixture is stirred for 1 hour at 20°C and is then washed twice with 50 cm^3 of water and dried over magnesium sulphate. The solution is filtered and concentrated to dryness under reduced pressure (2.7 kPa). The oil obtained is chromatographed on a silica gel column (0.04 mm-0.06 mm, diameter 2.8 cm, height 26 cm), eluting under a nitrogen pressure of 0.6 bar with a cyclohexane and ethyl acetate mixture of (60/40 by volume) and collecting fractions of 60 cm^3.

Fractions 6 to 20 are pooled and concentrated to dryness under reduced pressure (2.7 kPa) and the residue is crystallised from an acetonitrile and diisopropyl oxide mixture. The crystals are drained and dried. 2.16 g of (4aRS,7aRS)-6-[(2-dimethylamino-phenyl)acetyl]-4,4-diphenylperhydrothiopyrano[2,3-c]-pyrrole are obtained in the form of a white solid; melting point 163°C.

Example of Use 2

By carrying out the procedure as in Example of Use 1, using 1.85 g of [2-(1-pyrrolidinyl)phenyl]-acetic acid hydrobromide and 2.0 g of (4aRS,7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole hydrochloride, 0.90 g of (4aRS,7aRS)-6-{[2-(1-pyrrolidinyl)phenyl]acetyl}-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole is obtained in the form of white crystals; melting point 166°C.

Example of Use 3

A solution of 1.15 cm^3 of phenylacetyl chloride in 25 cm^3 of dichloromethane is added over 5 minutes to a solution, cooled to 0°C, of 2.63 g of (4aRS,7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]-pyrrole hydrochloride and 2.42 cm^3 of triethylamine in 25 cm^3 of dichloromethane. After stirring for one hour at 0°C and one hour at 20°C, 20 cm^3 of dichloromethane are added. The reaction mixture is washed twice with 100 cm^3 of distilled water, dried over magnesium

sulphate and then concentrated to dryness under reduced pressure (2.7 kPa). The oil obtained is chromatographed on a silica gel column (0.04-0.06 mm, diameter 3.5 cm, height 26 cm), eluting under a nitrogen pressure of 0.4 bar with a cyclohexane and ethyl acetate mixture (80/20 by volume) and collecting fractions of 125 cm^3. Fractions 19 to 26 are pooled and concentrated to dryness under reduced pressure (2.7 kPa). 0.87 g of (4aRS,7aRS)-6-phenylacetyl-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole is obtained in the form of a white solid; melting point 210°C.

Example of Use 4

0.58 cm^3 of ethyl chloroformate is added to a solution 0.92 g of 2-hydroxyphenylacetic in 30 cm^3 of dry dichloromethane. After stirring for 15 minutes at 20°C, the mixture is cooled to -15°C and 0.85 cm^3 of triethylamine is added. After stirring for 2 hours at -15°C, a suspension of 2 g of (4aRS,7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole hydrochloride and 1.70 cm^3 of triethylamine in 30 cm^3 of dichloromethane is added over 20 minutes. After stirring for 20 hours at 20°C, the reaction mixture is washed with 50 cm^3 of 1N hydrochloric acid and 50 cm^3 of a saturated aqueous solution of sodium chloride and then dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The residue is crystallised from 20 cm^3 of dichloromethane, the crystals are washed with diisopropyl oxide, drained and dried under reduced

pressure (2.7 kPa). 1.02 g of (4aRS,7aRS)-4,4-diphenyl-6-[(2-hydroxyphenyl)acetyl]perhydrothiopyrano[2,3-c]-pyrrole are obtained in the form of white crystals; melting point 248°C.

Example of Use 5

1.13 g of N,N'-carbonyldiimidazole are added to a solution, cooled to 0°C, of 1.16 g of 2-methoxyphenylacetic acid in 20 cm^3 of dry dichloromethane. The mixture is stirred for 40 minutes at 0°C and then a solution of 2.15 g of (4aRS,7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole hydrochloride and 0.9 cm^3 of triethylamine in 20 cm^3 of dichloromethane is added. The reaction mixture is stirred for one hour at 0°C and is then washed with a saturated aqueous solution of sodium hydrogen carbonate. The organic phase is dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The solid obtained is washed with 30 cm^3 of ethyl ether and 30 cm^3 of diisopropyl oxide and it is then dried under reduced pressure (2.7 kPa). 2.66 g of (4aRS,7aRS)-4,4-diphenyl-6-[(2-methoxyphenyl)acetyl]perhydrothiopyrano[2,3-c]pyrrole are obtained in the form of a white solid; melting point 172°C.

Example of Use 6

6-[(S)-2-(2-Methoxyphenyl)propionyl]-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole - mixture of the (4aR,7aR) and (4aS,7aS) forms, may be prepared by

carrying out the procedure as described in Example 5, using 0.89 g of (S)-2-(2-methoxyphenyl)propionic acid and (4aRS,7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]-pyrrole hydrochloride. 1.46 g of 6-[(S)-2-(2-methoxyphenyl)propionyl]-4,4-diphenylperhydrothiopyrano-[2,3-c]pyrrole - mixture of the (4aR,7aR) and (4aS,7aS) forms, are obtained in the form of a white meringue.

First form:

Infrared spectrum (characteristic bands cm^{-1}): 3095, 3055, 3025, 2950, 2930, 2875, 2835, 1630, 1595, 1490, 1565, 1425, 1240, 1030, 750, 700.

Proton NMR spectrum (DMSO-d_6 + CF_3COOD, a mixture of the two rotamers is observed at room temperature; characteristic signals):

1.15 and 1.20 (2d, J=7.5, 3H, CH_3); 2.1-2.9 (mt, 5H, 2 CH_2 at 5 and 3 + H at 4a); 3.36 and 3.8 (2s, 3H, OCH_3); 6.7 to 7.4 (mt, 14H, aromatics).

Second form:

Infrared spectrum (characteristic bands cm^{-1}): 3095, 3060, 3025, 2960, 2930, 2870, 2835, 1640, 1600, 1495, 1465, 1425, 1240, 1035, 755, 700.

Proton NMR spectrum (DMSO-d_6 + CF_3COOD, a mixture of the two rotamers is observed at room temperature; characteristic signals):

1.1 and 1.18 (2d, J=7.5, 3H, CH_3); 2.1-2.35 (mt, 2H, CH_2 at 3); 2.35-3.10 (mt, 3H, CH_2 at 5 + H at 4a); 3.6 and 3.8 (2s, 3H, OCH_3); 3.95 and 4.02 (mt, 1H, H at 7a); 6.7 to 7.4 (mt, 14H, aromatics).

(S)-2-(2-Methoxyphenyl)propionic acid may be obtained in the following manner:

(S)-2-(2-Methoxyphenyl)propionic acid may be prepared by analogy with the methods described by D.A Evans et al., Tetrahedron, 44, 5525, (1988), according to the following procedure:

1.52 g of lithium hydroxide are added to a solution, cooled to +5°C, of 4.1 g of (4S,5S)-4-methyl-5-phenyl-3-[(S)-2-(2-methoxyphenyl)propionyl]-2-oxazolidinone in 60 cm^3 of tetrahydrofuran and 30 cm^3 of water. The reaction mixture is stirred for 3 hours at this temperature and then, after returning to room temperature, ethyl acetate is added, the mixture decanted, the aqueous phase is acidified with a 1N aqueous solution of hydrochloric acid, extracted with ethyl acetate and the organic phase is dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The solid obtained is recrystallised from hexane, drained and dried. 0.4 g of (S)-2-(2-methoxyphenyl)propionic acid is obtained in the form of white crystals; melting point 102°C. $[\alpha]_D^{20}$ = +84.6°; (c=1; $CHCl_3$).

(4S,5S)-4-Methyl-5-phenyl-3-[(S)2-(2-methoxyphenyl)propionyl]-2-oxazolidinone may be obtained in the following manner:

19.1 g of sodium 1,1,1,3,3,3-hexamethyldisilazanate are added to a solution, cooled to -50°C, of 10 g of (4S,5S)-4-methyl-5-phenyl-3-[(2-methoxy-

phenyl)acetyl]-2-oxazolidinone in 150 cm^3 of tetrahydrofuran, the mixture is stirred for 45 minutes at this temperature and then 7.72 cm^3 of methyl iodide are added. The reaction mixture is then stirred for 15 hours at room temperature and then diluted with ethyl acetate, washed with 50 cm^3 of water and then with 50 cm^3 of a saturated aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is crystallised from isopropyl oxide, drained and dried. 4.2 g of (4S,5S)-4-methyl-5-phenyl-3-[(S)-2-(2-methoxyphenyl)propionyl]-2-oxazolidinone are obtained in the form of a white solid.

(4S,5S)-4-Methyl-5-phenyl-3-(2-methoxyphenylacetyl)-2-oxazolidinone may be obtained in the following manner:

9.38 g of 2-methoxyphenylacetic acid are added, at room temperature, to a suspension of 1.89 g of sodium hydride (80% dispersion in vaseline) in 200 cm^3 of dry tetrahydrofuran. This suspension is cooled to -30°C, 7.77 cm^3 of pivaloyl chloride are added and then a solution, cooled to -78°C, which is obtained by adding 35.27 cm^3 of a 1.6 M solution of butyllithium in hexane to a solution, cooled to -78°C, of 10 g of (4S,5S)-4-methyl-5-phenyl-2-oxazolidinone in 200 cm^3 of dry tetrahydrofuran, is finally added. The reaction mixture is stirred for 45 minutes at -30°C and then

after reequilibrating to room temperature, 200 cm^3 of a saturated aqueous solution of ammonium chloride is added followed by 500 cm^3 of ethyl acetate; after decantation, the organic phase is washed twice with 100 cm^3 of water and then twice with 100 cm^3 of a saturated aqueous solution of sodium chloride, dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 4.8 cm, height 36 cm), eluting under a nitrogen pressure of 0.6 bar with a cyclohexane and ethyl acetate mixture (85/15 and then 80/20 by volume) and collecting fractions of 50 cm^3. Fractions 14 to 31 are pooled and concentrated to dryness under reduced pressure (2.7 kPa). 13.6 g of (4S,5S)-4-methyl-5-phenyl-3-(2-methoxyphenylacetyl)-2-oxazolidinone are obtained in the form of a yellow oil.

Example of Use 7

By carrying out the procedure according to that described in Example 8 below, using 1.82 g of (1RS,4aRS,7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]-pyrrole 1-oxide and 1.39 g of [(3-dimethylamino-2-propoxy)phenyl]acetic acid, 0.3 g of (1RS,4aRS,7aRS)-6-{[(3-dimethylamino-2-propoxy)phenyl]acetyl}-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1-oxide is obtained in the form of white crystals; melting point 150°C.

Example of Use 8

0.03 g of hydroxybenzotriazole hydrate is added to a solution, cooled to 0°C, of 1.06 g of (1R*,4aR*,7aR*)-(-)-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1-oxide and 0.81 g of 2-[(3-dimethylamino-2-propoxy)phenyl]acetic acid in 60 cm^3 of dry dichloromethane, followed by 0.77 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide. After stirring for 2 hours at 0°C and 20 hours at 20°C, the reaction mixture is washed with 20 cm^3 of water and then dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The residue is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 2.4 cm, height 35 cm), eluting under a nitrogen pressure of 0.6 bar with an ethyl acetate, acetic acid and water mixture (60/10/10 by volume) and collecting fractions of 50 cm^3. Fractions 8 to 19 are pooled and concentrated to dryness under reduced pressure (2.7 kPa). The residue is taken up in 60 cm^3 of dichloromethane, the solution is washed with 20 cm^3 of a 1N aqueous solution of sodium hydroxide, dried over magnesium sulphate and then concentrated to dryness. The solid obtained is recrystallised from an ethyl acetate and ethyl ether mixture, the crystals are washed with diisopropyl oxide, drained and dried. 0.99 g of (1R*,4aR*,7aR*)-(-)-6-{2-[(3-dimethylamino-2-propoxy)phenyl]acetyl}-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1-oxide is obtained in the form of

a white solid; melting point 120°C. $[\alpha]_D^{20}$ = -323°; (c = 0.5; acetic acid).

Example of use 9

0.03 g of hydroxybenzotriazole hydrate is added to a solution, cooled to +5°C, of 0.69 g of (1RS,4aRS,7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]-pyrrole 1-oxide and 0.68 g of {[3-(1-pyrrolidinyl)-2-propoxy]phenyl}acetic acid in 25 cm^3 of dry dichloromethane, followed by a solution of 0.5 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride in 20 cm^3 of dry dichloromethane. After stirring for 2 hours at +5°C and 20 hours at 20°C, the reaction mixture is washed twice with 50 cm^3 of distilled water and dried over magnesium sulphate and then concentrated to dryness under reduced pressure (2.7 kPa). The residue obtained is chromatographed on a silica gel column (particle size 0.04-0.06 mm, diameter 2.4 cm, height 32 cm), eluting under a nitrogen pressure of 0.8 bar with an ethyl acetate, acetic acid and water mixture (80/20/20 by volume) and collecting fractions of 25 cm^3. Fractions 21 to 50 are pooled and concentrated to dryness under reduced pressure (2.7 kPa). The residue is crystallised from 8 cm^3 of ethyl acetate, the crystals are washed with ethyl acetate and diisopropyl oxide and then dried. 0.45 g of (1RS,4aRS,7aRS)-6-{{[3-(1-pyrrolidinyl)-2-propoxy]-phenyl}acetyl}-4,4-diphenylperhydrothiopyrano[2,3-c]-pyrrole 1-oxide is obtained in the form of beige

crystals; melting point 126°C.

Example of Use 10

0.06 g of hydroxybenzotriazole hydrate and 1.01 g of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride are added to a solution, cooled to about 0°C, of 1.43 g of (1R*,4aR*,7aR*)-(-)-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1-oxide and 0.83 g of (S)-2-(2-methoxyphenyl)propionic acid in 100 cm^3 of dry dichloromethane. After stirring for 2 hours at 0°C and 2 hours at 20°C, the reaction mixture is washed with 50 cm^3 of water and then dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The residue is crystallised from acetonitrile, the crystals are drained, washed several times with ethyl ether and then dried.

1.56 g of (1R*,4aR*,7aR*)-(-)-6-[(S)-2-(2-methoxyphenyl)propionyl]-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1-oxide are obtained in the form of white crystals; melting point 170°C. $[\alpha]_D^{20}$ = -316°; (c = 0.50; acetic acid).

Example of Use 11

By carrying out the procedure as described in Example 1 above, using 0.49 g of 2-dimethylaminophenylacetic acid, 0.50 g of N,N'-carbonyldiimidazole, 0.70 cm^3 of triethylamine and 1.0 g of (4aRS,7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1,1-dioxide hydrochloride, 0.55 g of (4aRS,7aRS)-6-[(2-dimethylaminophenyl)acetyl]-4,4-diphenylperhydro-

thiopyrano[2,3-c]pyrrole 1,1-dioxide is obtained in the form of white crystals; melting point 226°C.

Example of Use 12

0.35 cm^3 of triethylamine and a solution of 0.17 cm^3 of phenylacetyl chloride in 5 cm^3 of dichloromethane are added to a suspension, cooled to 0°C, of 0.46 g of (4aRS,7aRS)-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1,1-dioxide hydrochloride in 10 cm^3 of dichloromethane. After stirring for 1 hour at 0°C and then 1 hour at 20°C, the reaction mixture is diluted with 10 cm^3 of dichloromethane, washed twice with 30 cm^3 of distilled water, dried over magnesium sulphate and concentrated to dryness under reduced pressure (2.7 kPa). The oil obtained is crystallised from 30 cm^3 of ethyl ether, the crystals are drained and dried. 0.50 g of (4aRS,7aRS)-4,4-diphenyl-6-phenylacetylperhydrothiopyrano[2,3-c]pyrrole 1,1-dioxide is obtained in the form of white crystals.

Infrared spectrum (characteristic bands cm^{-1}): 3050, 3025, 2970, 2930, 1880, 1630, 1595, 1495, 1455, 1425, 1330, 1305, 1140, 1120, 765, 755, 700, 510.

Proton NMR spectrum (DMSO-d_6 + CF_3COOD, main signals, a mixture of the two rotamers is observed at room temperature): 2.48 (mt, 1H, CH_2 at 3); 2.8 (mt, 1H, 1H at 5); 3.39 and 3.65 (s and ab J=14, 2H, N-CO-CH_2); 6.9 to 7.6 (mt, 15H, aromatics).

Example of Use 13

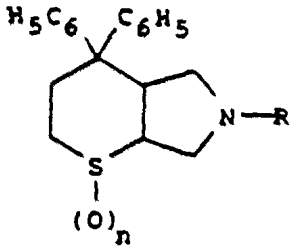
1.16 cm^3 of triethylamine are added dropwise

to a suspension of 1.5 g of (4aRS,7aRS)-4,4-diphenyl-perhydrothiopyrano[2,3-c]pyrrole 1,1-dioxide hydrochloride and 0.95 g of 1-ethoxy-1-imino-2-(2-methoxyphenyl)ethyl hydrochloride in 15 cm^3 of 1,2-dichloroethane. After stirring for 20 hours at 20°C, 30 cm^3 of dichloromethane are added to the mixture and it is then washed successively with 100 cm^3 of water and 100 cm^3 of a 5% aqueous solution of potassium carbonate. The organic phase is dried over magnesium sulphate, and concentrated to dryness under reduced pressure (2.7 kPa). The residue is crystallised from an acetonitrile and diisopropyl oxide mixture. The crystals are washed with acetonitrile and then with diisopropyl oxide, drained and dried. 0.83 g of (4aRS,7aRS)-1-imino-2-(2-methoxyphenyl)-6-ethyl-4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole 1,1-dioxide is obtained in the form of white crystals; melting point 240°C.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated integer or group of integers but not the exclusion of any other integer or group of integers.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A thiopyranopyrrole derivative characterised in that it is of the general formula:



in which the symbol R represents a hydrogen atom, an allyl radical, a vinyloxycarbonyl radical, a tert-butoxy carbonyl radical, or a radical of the structure:

$$-CR_aR_bR_c$$

in which R_a and R_b are hydrogen atoms or phenyl radicals which are optionally substituted (by a halogen atom, an alkyl, alkoxy or nitro radical), and R_c is defined as R_a and R_b or represents an alkyl or alkoxyalkyl radical, at least one of R_a, R_b and R_c being a substituted or unsubstituted phenyl radical, and the symbol n represents an integer from 0 to 2, it being understood that the abovementioned alkyl radicals contain 1 to 4 carbon atoms in a linear or branched chain, as well as its stereoisomeric forms and its salts when these exist.

2. A thiopyranopyrrole derivative according to Claim 1, characterised in that it is 4,4-diphenylperhydrothiopyrano[2,3-c]pyrrole, as well as its salts, in its stereoisomeric forms and mixtures thereof.

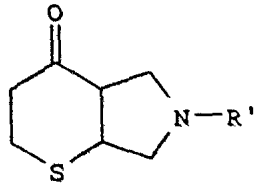
3. A thiopyranopyrrole derivative according to Claim 1, characterised in that it is 4,4-diphenyl-perhydrothiopyrano[2,3-c]pyrrole 1-oxide, as well as its salts, in its stereoisomeric forms and mixtures thereof.

4. A thiopyranopyrrole derivative according to Claim 1, characterised in that it is 4,4-diphenyl-perhydrothiopyrano[2,3-c]pyrrole 1,1-dioxide, as well as its salts, in its stereoisomeric forms and mixtures thereof.

5. A thiopyranopyrrole derivative according to Claim 1, characterised in that it is 4,4-diphenyl-6-vinyloxycarbonylperhydrothiopyrano[2,3-c]pyrrole in its stereoisomeric forms and mixtures thereof.

6. A thiopyranopyrrole derivative according to Claim 1, characterised in that it is 4,4-diphenyl-6-tert-butyloxycarbonylperhydrothiopyrano[2,3-c]pyrrole 1-oxide in its stereoisomeric forms and mixtures thereof.

7. Method of preparing a thiopyranopyrrole derivative according to Claim 1, characterised in that a derivative of general formula:



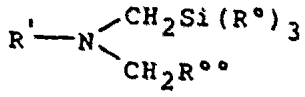
in which R' is defined as R in Claim 1 except for

representing a hydrogen atom, is treated successively with a phenylmagnesium halide, and then with benzene in the presence of zirconium tetrachloride, and then the protective radical R' is optionally removed if it is desired to obtain a product for which R is a hydrogen atom, and/or, where appropriate, the product obtained is oxidised in order to obtain a thiopyranopyrrole derivative for which n = 1 or 2, and then the stereoisomers are optionally separated and the product obtained is optionally converted to a salt when these exist.

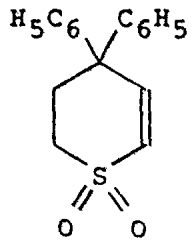
8. Method of preparing a thiopyranopyrrole derivative according to Claim 1, for which the symbol n is equal to 1 or 2, characterised in that a thiopyranopyrrole derivative according to Claim 1, for which the symbol n is equal to 0 and, when appropriate, whose amine functional group is protected beforehand, is oxidised by any known method for the oxidation of sulphides to sulphoxides or to sulphones, which does not affect the rest of the molecule and then, where appropriate, if it is desired to obtain a product for which R is a hydrogen atom, the protective radical is removed, the stereoisomers are optionally separated and the product obtained is optionally converted to a salt when these exist.

9. Method of preparing a thiopyranopyrrole derivative according to Claim 1, for which the symbol n

is equal to 2, characterised in that a cycloaddition reaction of a silylated derivative of general formula:

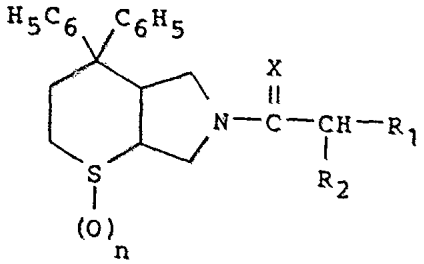


in which in which R' is defined as above, $(R^{\circ})_3$ represents alkyl radicals or alkyl and phenyl radicals and $R^{\circ\circ}$ represents an alkoxy, cyano or phenylthio radical, with 3,4-dihydro-4,4-diphenyl-2H-thiapyran 1,1-dioxide of formula:



is carried out followed optionally by the removal of the protective radical R' if it is desired to obtain a thiopyranopyrrole derivative according to Claim 1, for which R is a hydrogen atom, and then the stereoisomers are optionally separated and the product obtained is optionally converted to a salt when these exist.

10. Use of a product according to Claim 1, for the preparation of a thiopyranopyrrole derivative of general formula:



in which:

- the symbol n is an integer from 0 to 2,
- the symbol X represents an oxygen atom, or an NH radical,
- the symbol R_1 represents a phenyl radical which is optionally substituted by one or more halogen atoms or hydroxyl or alkyl radicals which may be optionally substituted (by halogen atoms or amino, alkylamino or dialkylamino radicals) alkoxy or alkylthio radicals which may be optionally substituted [by hydroxyl, amino, alkylamino or dialkylamino radicals optionally substituted (by phenyl, hydroxyl or amino radicals), or by dialkylamino radicals whose alkyl parts form with the nitrogen atom to which they are attached, a heterocycle with 5 to 6 members which may contain another heteroatom chosen from oxygen, sulphur or nitrogen, optionally substituted (by an alkyl, hydroxyl or hydroxyalkyl radical)], or which is substituted by amino, alkylamino or dialkylamino radicals whose alkyl parts may form with the nitrogen atom to which they are attached, a heterocycle such as defined above, or represents a cyclohexadienyl, naphthyl or a saturated or unsaturated, mono- or polycyclic heterocyclic radical containing 5 to 9 carbon atoms and one or more heteroatoms chosen from oxygen, nitrogen or sulphur, and

- the symbol R_2 represents a hydrogen or halogen atom or a hydroxyl, alkyl, aminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, alkylthio, acyloxy, carboxyl, alkoxycarbonyl, dialkylaminoalkoxycarbonyl, benzyloxycarbonyl, amino, acylamino or alkoxycarbonylamino radical, the abovementioned alkyl and acyl radicals being linear or branched and containing 1 to 4 carbon atoms, in its stereoisomeric forms or mixtures thereof, as well as its salts when these exist.

11. A thiopyranopyrrole derivative according to claim 1 or a use thereof substantially as hereinbefore described with reference to the examples.

12. A method according to any one of claims 7 to 9 substantially as hereinbefore described with reference to the examples.

DATED this 22nd day of July, 1994.

RHONE-POULENC RORER S.A.
By Its Patent Attorneys
DAVIES COLLISON CAVE

INTERNATIONAL SEARCH REPORT

International application No.
PCT/FR 92/00432

A. CLASSIFICATION OF SUBJECT MATTER

Int.Cl.5 C07D495/04; //(C07D495/04, 335:00, 209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Int.Cl.5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US, A, 4 042 707 (W.C.RIPKA) 16 August 1977 cited in the application * column 31, table I *	1
A	EP, A, 0 068 822 (ROHM AND HAAS CO.) 5 January 1983 cited in the application see abstract	1
A	AU, B, 502 760 (SCIENCE UNION ET CIE.) 9 August 1979 see claims 1,2	1
A	EP, A, 0 359 172 (SHIONOGI AND CO., LTD.)21 March 1990 * page 15; compound (II-11) *	1
A	EP, A, 0 058 567 (WARNER-LAMBERT CO.) 25 August 1982 see abstract	10
A	EP, A, 0 093 805 (WARNER-LAMBERT CO.) 16 November 1983 see abstract	10

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 August 1992 (21.08.92)	7 September 1992 (07.09.92)
Name and mailing address of the ISA/ EUROPEAN PATENT OFFICE Facsimile No.	**Authorized officer** Telephone No.

Form PCT/ISA/210 (second sheet) (July 1992)

RAPPORT DE RECHERCHE INTERNATIONALE

Demande internationale No PCT/FR 92/00432

I. CLASSEMENT DE L'INVENTION (si plusieurs symboles de classification sont applicables, les indiquer tous) [7]

Selon la classification internationale des brevets (CIB) ou à la fois selon la classification nationale et la CIB

CIB 5 C07D495/04; //(C07D495/04,335:00,209:00)

II. DOMAINES SUR LESQUELS LA RECHERCHE A PORTE

Documentation minimale consultée[8]

Système de classification	Symboles de classification
CIB 5	C07D

Documentation consultée autre que la documentation minimale dans la mesure où de tels documents font partie des domaines sur lesquels la recherche a porté[9]

III. DOCUMENTS CONSIDERES COMME PERTINENTS[10]

Catégorie °	Identification des documents cités, avec indication, si nécessaire[12], des passages pertinents[13]	No. des revendications visées[14]
A	US,A,4 042 707 (W.C. RIPKA) 16 Août 1977 cité dans la demande * colonne 31, tableau I *	1
A	EP,A,0 068 822 (ROHM AND HAAS CO.) 5 Janvier 1983 cité dans la demande voir abrégé	1
A	AU,B,502 760 (SCIENCE UNION ET CIE.) 9 Août 1979 voir revendications 1,2	1
A	EP,A,0 359 172 (SHIONOGI AND CO., LTD.) 21 Mars 1990 * page 15, composé (II-11) *	1
A	EP,A,0 058 567 (WARNER-LAMBERT CO.) 25 Août 1982 voir abrégé	10

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° Catégories spéciales de documents cités:[11]

"A" document définissant l'état général de la technique, non considéré comme particulièrement pertinent

"E" document antérieur, mais publié à la date de dépôt international ou après cette date

"L" document pouvant jeter un doute sur une revendication de priorité ou cité pour déterminer la date de publication d'une autre citation ou pour une raison spéciale (telle qu'indiquée)

"O" document se référant à une divulgation orale, à un usage, à une exposition ou tous autres moyens

"P" document publié avant la date de dépôt international, mais postérieurement à la date de priorité revendiquée

"T" document ultérieur publié postérieurement à la date de dépôt international ou à la date de priorité et n'appartenant pas à l'état de la technique pertinent, mais cité pour comprendre le principe ou la théorie constituant la base de l'invention

"X" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme nouvelle ou comme impliquant une activité inventive

"Y" document particulièrement pertinent; l'invention revendiquée ne peut être considérée comme impliquant une activité inventive lorsque le document est associé à un ou plusieurs autres documents de même nature, cette combinaison étant évidente pour une personne du métier.

"&" document qui fait partie de la même famille de brevets

IV. CERTIFICATION

Date à laquelle la recherche internationale a été effectivement achevée	Date d'expédition du présent rapport de recherche internationale
21 AOUT 1992	07 SEP 1992

Administration chargée de la recherche internationale	Signature du fonctionnaire autorisé
OFFICE EUROPEEN DES BREVETS	CHRISTIAN HASS

ANNEXE AU RAPPORT DE RECHERCHE INTERNATIONALE RELATIF A LA DEMANDE INTERNATIONALE NO.

FR 9200432
SA 60084

La présente annexe indique les membres de la famille de brevets relatifs aux documents brevets cités dans le rapport de recherche internationale visé ci-dessus.
Lesdits membres sont contenus au fichier informatique de l'Office européen des brevets à la date du 21/08/92
Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office européen des brevets.

Document brevet cité au rapport de recherche	Date de publication	Membre(s) de la famille de brevet(s)		Date de publication
US-A-4042707	16-08-77	Aucun		
EP-A-0068822	05-01-83	US-A-	4439229	27-03-84
		JP-A-	58013567	26-01-83
AU-B-502760	09-08-79	AU-A-	2277977	16-06-77
EP-A-0359172	21-03-90	JP-A-	2078659	19-03-90
		US-A-	5017708	21-05-91
EP-A-0058567	25-08-82	AT-T-	8619	15-08-84
		EP-A,B	0093805	16-11-83
		JP-A-	57158758	30-09-82
		US-A-	4503043	05-03-85
EP-A-0093805	16-11-83	AT-T-	8619	15-08-84
		EP-A,B	0058567	25-08-82
		JP-A-	57158758	30-09-82
		US-A-	4503043	05-03-85

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