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The present invention relates to N-substituted heterocyclic derivatives, to their preparation and to the pharmaceutical compositions in which they are present.

05 The compounds according to the invention antagonize the action of angiotensin II, which is a peptide hormone of the formula

H-Asp-Arg-Val-Tyr-Ile-His-Pro-Phe-OH

10 Angiotensin II is a potent vasopressor and the biologically active product of the renin-angiotensin system: renin acts on the angiotensinogen of the plasma to produce angiotensin I, which is converted to angiotensin II by the action of the angiotensin I converting enzyme.

15 The compounds of the present invention are non-peptide compounds which antagonize angiotensin II. By inhibiting the action of angiotensin II on its receptors, the compounds according to the invention prevent especially the increase in blood pressure produced by
20 the hormone-receptor interaction; they also have other physiological actions on the central nervous system.

 Thus the compounds according to the invention are useful in the treatment of cardiovascular complaints such as hypertension and heart failure, as well
25 as in the treatment of complaints of the central nervous system and in the treatment of glaucoma and diabetic retinopathy.

 The present invention relates to compounds of the formula

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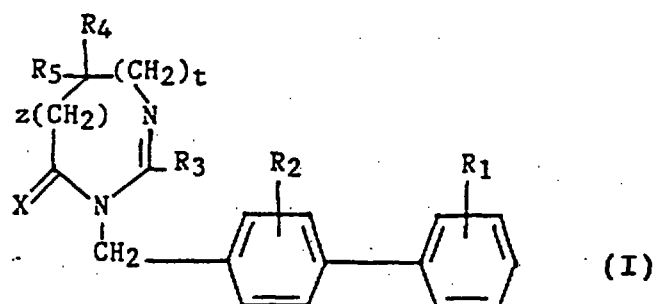
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in which:

- 10 - R_1 and R_2 are similar or different and are each independently hydrogen or a group selected from a C_1-C_6 alkyl, a C_1-C_4 alkoxy, an amino, an aminomethyl, a carboxyl, an alkoxycarbonyl in which the alkoxy is C_1-C_4 , a cyano, a tetrazolyl, a methyltetrazolyl, a
- 15 methylsulfonylamino, a trifluoromethylsulfonylamino, a trifluoromethylsulfonylaminomethyl, an N-cyanoacetamide, an N-hydroxyacetamide, an N-(4-carboxy-1,3-thiazol-2-yl)acetamide, a ureido, a 2-cyanoguanidinocarbonyl, a 2-cyanoguanidinomethyl, an imidazol-1-ylcarbonyl and a 3-cyano-2-methylisothio-
- 20 ureidomethyl, with the proviso that at least one of the substituents R_1 or R_2 is other than hydrogen;
- R_3 is a hydrogen, a C_1-C_6 alkyl which is unsubstituted or substituted by one or more halogen atoms, a
- 25 C_2-C_6 alkenyl, a C_3-C_7 cycloalkyl, a phenyl, a phenylalkyl in which the alkyl is C_1-C_3 , or a phenylalkenyl in which the alkenyl is C_2-C_3 , said phenyl groups being unsubstituted or monosubstituted or polysubstituted by a halogen atom, a C_1-C_4 alkyl, a
- 30 C_1-C_4 halogenoalkyl, a C_1-C_4 polyhalogenoalkyl, a hydroxyl or a C_1-C_4 alkoxy;
- R_4 and R_5 are each independently a C_1-C_6 alkyl, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3 , said alkyl, phenyl and phenylalkyl groups being
- 35 unsubstituted or substituted by one or more halogen



atoms or by a group selected from a C_1-C_4 perfluoroalkyl, a hydroxyl and a C_1-C_4 alkoxy;

- or R_4 and R_5 together form a group of the formula $=CR_7R_8$, in which R_7 is hydrogen, a C_1-C_4 alkyl or a phenyl and R_8 is a C_1-C_4 alkyl or a phenyl;
- or else R_4 and R_5 together are either a group of the formula $(CH_2)_n$ or a group of the formula $(CH_2)_pY(CH_2)_q$, in which Y is either an oxygen atom, or a sulfur atom, or a carbon atom substituted by a C_1-C_4 alkyl group, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3 , or a group $N-R_6$, in which R_6 is a hydrogen, a C_1-C_4 alkyl, a phenylalkyl in which the alkyl is C_1-C_3 , a C_1-C_4 alkylcarbonyl, a C_1-C_4 halogenoalkylcarbonyl, a C_1-C_4 polyhalogenoalkylcarbonyl, a benzoyl, an alpha-aminoacyl or an N-protecting group, or R_4 and R_5 , together with the carbon atom to which they are bonded, form an indane or an adamantane;
- $p + q = m$;
- n is an integer between 2 and 11;
- m is an integer between 2 and 5;
- X is an oxygen atom or sulfur atom; and
- z and t are zero or one is zero and the other is one; and their salts.

If a compound according to the invention has an asymmetric carbon, the invention includes the 2 optical isomers of this compound.

The salts of the compounds of formula (I) according to the present invention include those with mineral or organic acids which permit separation or suitable crystallization of the compounds of formula (I), such as picric acid, oxalic acid or an optically active acid, for example a mandelic acid or a camphorsulfonic acid, and acids which form pharmaceutically acceptable salts such as the hydrochloride, the hydro-



bromide, the sulfate, the hydrogensulfate, the dihydrogenphosphate, the methanesulfonate, the methylsulfate, the maleate, the fumarate and the naphthalene-2-sulfonate.

05 The salts of the compounds of formula (I) also include the salts with organic or mineral bases, for example the salts of alkali or alkaline earth metals, such as the sodium, potassium and calcium salts, the sodium and potassium salts being preferred, or with a
10 tertiary amine such as trometamol, or else the salts of arginine, lysine or any physiologically acceptable amine.

 According to the present description and in the claims which follow, halogen atom is understood as
15 meaning a bromine, chlorine or fluorine atom; N-protecting group (also designated by Pr) is understood as meaning a group conventionally used in peptide chemistry for affording temporary protection of the amine group, for example a Boc, Z or Fmoc group or a benzyl
20 group; esterified carboxyl group is understood as meaning an ester which is labile under appropriate conditions, such as, for example, a methyl, ethyl, benzyl or tert-butyl ester. "Alkyl" denotes linear or branched saturated aliphatic hydrocarbon radicals.

25 The compounds of formula (I) in which R_1 is in the ortho position and is a carboxyl or tetrazolyl group and R_2 is hydrogen are preferred compounds.

 The compounds of formula (I) in which R_4 and R_5 together form, with the carbon to which they are
30 bonded, a cyclopentane or a cyclohexane are preferred compounds.

 Likewise, the compounds of formula (I) in which R_3 is a linear C_1-C_6 alkyl group are preferred compounds.

35 The compounds of formula (I) in which X is an

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oxygen atom are also preferred compounds.

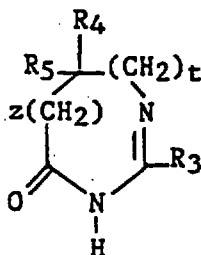
Finally, the compounds of formula (I) in which $z = t = 0$ are preferred compounds.

The following abbreviations are used in the description and in the Examples:

05	Et	: ethyl
	nBu, tBu	: n-butyl, tert-butyl
	DMF	: dimethylformamide
	THF	: tetrahydrofuran
10	DCM	: dichloromethane
	NBS	: N-bromosuccinimide
	DCC	: dicyclohexylcarbodiimide
	DIPEA	: diisopropylethylamine
	ether	: ethyl ether
15	TFA	: trifluoroacetic acid
	Z	: benzyloxycarbonyl
	Boc	: tert-butoxycarbonyl
	BOP	: benzotriazolyloxytrisdimethylaminophosphonium hexafluorophosphate
20	Fmoc	: fluorenylmethoxycarbonyl

The present invention further relates to the method of preparing the compounds (I). Said method is characterized in that:

a) a heterocyclic derivatives of the formula



in which z , t , R_3 , R_4 and R_5 are as defined above for (I), is reacted with a (biphenyl-4-yl)methyl derivative of the formula

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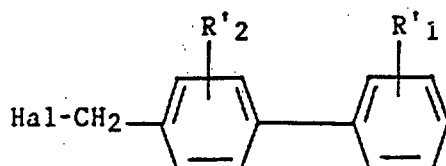
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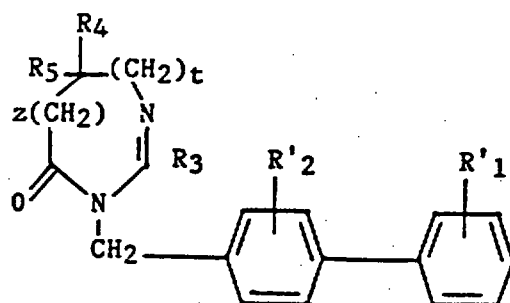
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in which Hal is a halogen atom and R'_1 and R'_2 are respectively either R_1 and R_2 or a precursor group of R_1 and R_2 ;

b1) if appropriate, the resulting compound of the formula

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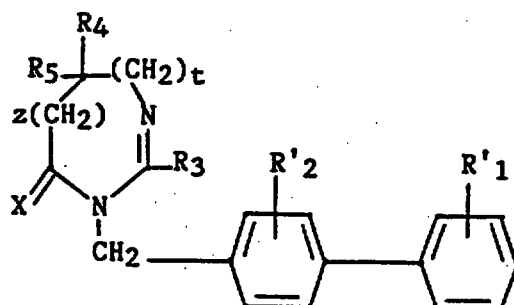


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20 is treated with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide]; and

c1) the compound obtained in a1) or b1), of the formula

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in which X is an oxygen atom or a sulfur atom, is treated to give the compound (I) by conversion of the

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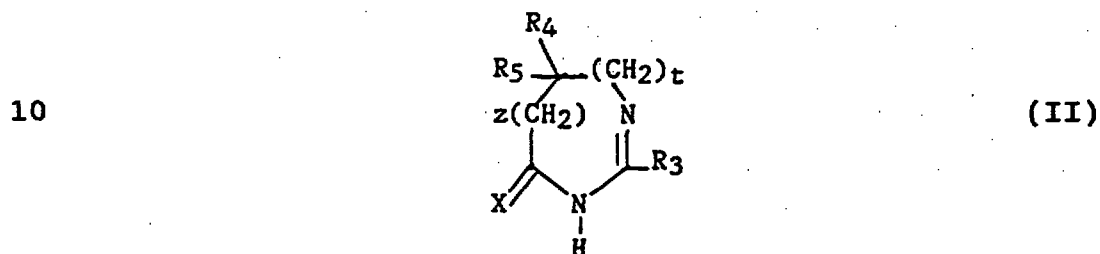


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groups R'_1 and/or R'_2 to the groups R_1 and/or R_2 respectively.

Among the compounds 2, the compounds (II) as defined below are novel.

05 Thus the present invention further relates to the compounds (II) of the formula



15 in which:

- R_3 is a hydrogen, a C_1-C_6 alkyl which is unsubstituted or substituted by one or more halogen atoms, a C_2-C_6 alkenyl, a C_3-C_7 cycloalkyl, a phenyl, a phenylalkyl in which the alkyl is C_1-C_3 , or a phenylalkenyl in which the alkenyl is C_2-C_3 , said phenyl groups being unsubstituted or monosubstituted or polysubstituted by a halogen atom, a C_1-C_4 alkyl, a C_1-C_4 halogenoalkyl, a C_1-C_4 polyhalogenoalkyl, a hydroxyl or a C_1-C_4 alkoxy;
- 20 - R_4 and R_5 are each independently a C_1-C_6 alkyl, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3 , said alkyl, phenyl and phenylalkyl groups being unsubstituted or substituted by one or more halogen atoms or by a group selected from a C_1-C_4 perfluoroalkyl, a hydroxyl and a C_1-C_4 alkoxy;
- 30 - or R_4 and R_5 together form a group of the formula $=CR_7R_8$, in which R_7 is hydrogen, a C_1-C_4 alkyl or a phenyl and R_8 is a C_1-C_4 alkyl or a phenyl;
- or else R_4 and R_5 together are either a group of the
- 35 formula $(CH_2)_n$ or a group of the formula $(CH_2)_pY-$



05 (CH₂)_q, in which Y is either an oxygen atom, or a sulfur atom, or a carbon atom substituted by a C₁-C₄ alkyl group, a phenyl or a phenylalkyl in which the alkyl is C₁-C₃, or a group N-R₆, in which R₆ is a hydrogen, a C₁-C₄ alkyl, a phenylalkyl in which the alkyl is C₁-C₃, a C₁-C₄ alkylcarbonyl, a C₁-C₄ halogenoalkylcarbonyl, a C₁-C₄ polyhalogenoalkylcarbonyl, a benzoyl, an alpha-aminoacyl or an N-protecting group, or R₄ and R₅, together with the carbon atom to
10 which they are bonded, form an indane or an adamantane;

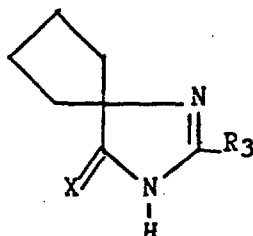
- p + q = m;
- n is an integer between 2 and 11;
- m is an integer between 2 and 5;
- 15 - X is an oxygen atom or sulfur atom; and
- z and t are zero or one is zero and the other is one; with the limitation that
 - if z and t are zero and X is an oxygen atom, R₄ and R₅ are other than
 - 20 • a C₁-C₆ alkyl, a phenyl or a phenylalkyl in which the alkyl is C₁-C₃, said alkyl, phenyl and phenylalkyl groups being unsubstituted or substituted by one or more halogen atoms or by a group selected from a C₁-C₄ perfluoroalkyl, a hydroxyl and a C₁-C₄ alkoxy;
 - 25 • or R₄ and R₅ together are other than a group N-R₆ in which R₆ is a hydrogen, a C₁-C₄ alkyl or a phenylalkyl in which the alkyl is C₁-C₃; and
 - n is other than 6;
- 30 and
- if z = 1 and R₃ is a phenyl, R₄ and R₅ are each other than a methyl.

Among the derivatives (II), the compounds in which z = t = 0 and R₄ and R₅, together with the carbon
35 to which they are bonded, form a cyclopentane are pre-

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ferred compounds. These compounds have the formula

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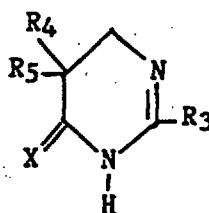


(II')

- 10 in which X is an oxygen atom or a sulfur atom and R_3 is
a hydrogen, a C_1 - C_6 alkyl which is unsubstituted or
substituted by one or more halogen atoms, a C_2 - C_6
alkenyl, a C_3 - C_7 cycloalkyl, a phenyl, a phenylalkyl in
15 which the alkyl is C_1 - C_3 , or a phenylalkenyl in which
the alkenyl is C_2 - C_3 , said phenyl groups being unsub-
stituted or monosubstituted or polysubstituted by a
halogen atom, a C_1 - C_4 alkyl, a C_1 - C_4 halogenoalkyl, a
 C_1 - C_4 polyhalogenoalkyl, a hydroxyl or a C_1 - C_4 alkoxy.

20 The compounds (II) in which $z = 0$ and $t = 1$, of
the formula

25



(II'')

in which R_3 , R_4 , R_5 and X are as defined above for
(II), are preferred compounds.

30 Finally, the compounds (II) in which $z = 1$ and
 $t = 0$, of the formula

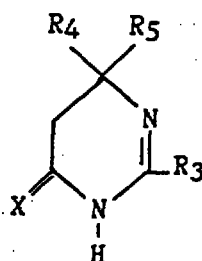
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(II''')

in which:

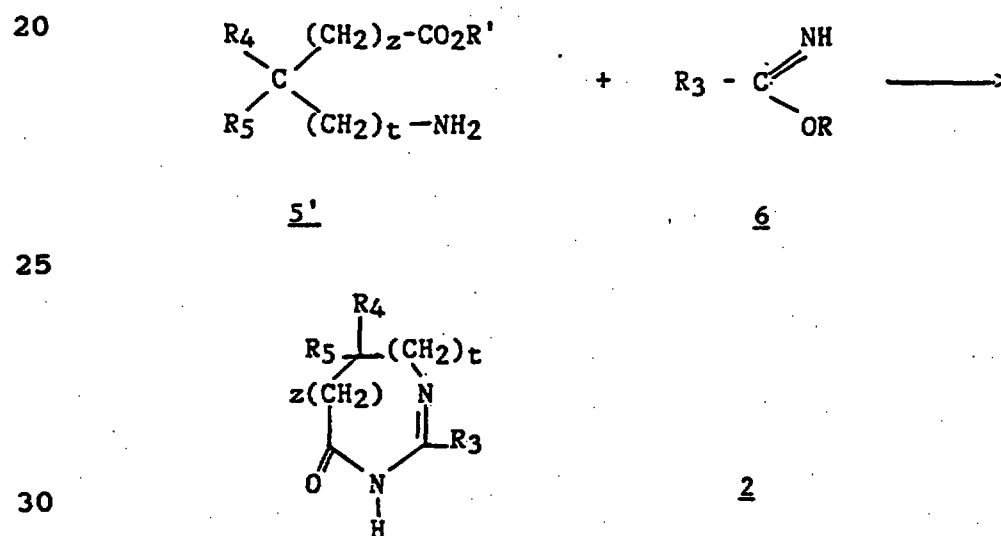
- R_3 is a hydrogen, a C_1-C_6 alkyl which is unsubstituted or substituted by one or more halogen atoms, a C_2-C_6 alkenyl, a C_3-C_7 cycloalkyl, a phenyl, a phenylalkyl in which the alkyl is C_1-C_3 , or a phenylalkenyl in which the alkenyl is C_2-C_3 , said phenyl groups being unsubstituted or monosubstituted or polysubstituted by a halogen atom, a C_1-C_4 alkyl, a C_1-C_4 halogenoalkyl, a C_1-C_4 polyhalogenoalkyl, a hydroxyl or a C_1-C_4 alkoxy;
- R_4 and R_5 are each independently a C_1-C_6 alkyl, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3 , said alkyl, phenyl and phenylalkyl groups being unsubstituted or substituted by one or more halogen atoms or by a group selected from a C_1-C_4 perfluoroalkyl, a hydroxyl and a C_1-C_4 alkoxy;
- or R_4 and R_5 together form a group of the formula $=CR_7R_8$, in which R_7 is hydrogen, a C_1-C_4 alkyl or a phenyl and R_8 is a C_1-C_4 alkyl or a phenyl;
- or R_4 and R_5 together are either a group of the formula $(CH_2)_n$ or a group of the formula $(CH_2)_pY-(CH_2)_q$, in which Y is either an oxygen atom, or a sulfur atom, or a carbon atom substituted by a C_1-C_4 alkyl group, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3 , or a group $N-R_6$, in which R_6 is a hydrogen, a C_1-C_4 alkyl, a phenylalkyl in which the alkyl is C_1-C_4 , a C_1-C_4 alkylcarbonyl, a C_1-C_4 halogenoalkylcarbonyl, a C_1-C_4 polyhalogenoalkylcarbonyl,

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a benzoyl, an alpha-aminoacyl or an N-protecting group, or R_4 and R_5 , together with the carbon atom to which they are bonded, form an indane or an adamantane;

- 05 - $p + q = m$;
 - n is an integer between 2 and 11;
 - m is an integer between 2 and 5; and
 - X is an oxygen atom or a sulfur atom;
 with the limitation that R_3 is other than a phenyl if
 10 R_4 and R_5 are each a methyl,
 are preferred compounds.

The derivatives 2 are prepared by known methods. For example, it is possible to use the method described by Jacquier et al. (Bull. Soc. Chim. France, 1971, 3, 1040-1051) and by Brunken and Bach (Chem. Ber., 1956, 89, 1363-1373) and to react an alkyl imidate with an amino acid or its ester in accordance with the following reaction scheme:



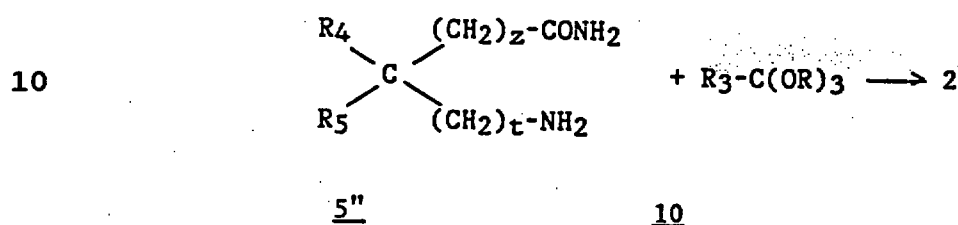
in which R is a C₁-C₄ alkyl, R' is hydrogen or a C₁-C₄ alkyl and R₃, R₄, R₅, z and t are as defined above for (I).



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This reaction is carried out in an acid medium by heating in an inert solvent such as xylene or toluene.

According to another procedure, the compound 2 can be prepared by reacting an aminoalkylamide (5'') with an alkyl ortho-ester (10) in an acid medium in accordance with the following reaction scheme:



in which R is a C₁-C₄ alkyl.

Using a procedure described by H. Takenaka et al. (Heterocycles, 1989, 29(6), 1185-89), it is also possible to prepare the compound 2 by reacting an acid halide of the formula

20



in which Hal is a halogen, preferably chlorine, with the derivative 5''.

25

The reaction is carried out in a basic medium.

More particularly, according to another object of the present invention, the compound 2 is prepared by a method characterized in that it comprises reacting a compound of the formula

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in which B is

- a group C(OR)₃

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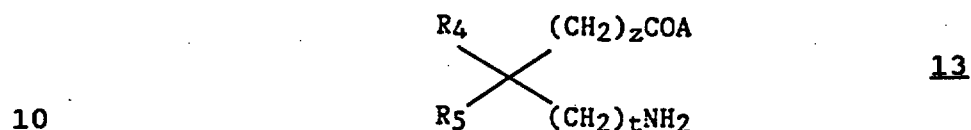


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- a group $\begin{array}{c} \text{NH} \\ \text{C} \\ \text{OR} \end{array}$ or

- a group COHal

05 R being a C₁-C₄ alkyl and Hal denoting a halogen atom, preferably chlorine, with a compound of the formula



in which A is an OH group, an NH₂ group or a group OR', R' being hydrogen or a C₁-C₄ alkyl, and then, if appropriate, treating the resulting compound with
15 Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane disulfide).

The (biphenyl-4-yl)methyl derivative (3) is prepared by a method described in European patent application 324 377.

20 The conversion of a group R'₁ and/or R'₂ to a group R₁ and/or R₂ is effected by methods well known to those skilled in the art. Thus, if the compound (I) to be prepared possesses a group R₁ and/or R₂ = carboxyl, R'₁ and/or R'₂ are an esterified carboxyl group. If
25 the compound (I) to be prepared possesses a group R₁ and/or R₂ = tetrazolyl, R'₁ and/or R'₂ can be either a tetrazolyl protected for example by a trityl group, or a cyano group which will subsequently be replaced with a tetrazolyl group protected if necessary by a trityl.
30 The conversion of the cyano group to a tetrazolyl can be effected with an azide, for example tributyltin azide or sodium azide.

It is also possible to use groups R'₁ and/or R'₂ such as nitro, carboxyl, cyano or acid chloride
35 groups and then to convert them by reactions well known



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to those skilled in the art to give groups R_1 and/or R_2 as defined for the compound (I).

Thus, if R'_1 and/or R'_2 are a carboxyl, they can be converted to R_1 and/or R_2 in the form of an
05 imidazol-1-ylcarbonyl or else an N-(4-carboxy-1,3-thiazol-2-yl)acetamide.

The group R'_1 and/or R'_2 in the form of an acid chloride can be converted to R_1 and/or R_2 in the form of N-hydroxyacetamide, N-cyanoacetamide, ureido or 2-
10 cyanoguanidinocarbonyl.

The group R'_1 and/or R'_2 in the form of a nitro can be converted to amino, from which R_1 and/or R_2 is prepared in the form of methylsulfonylamino, trifluoromethylsulfonylamino or trifluoromethylsulfonylamino-
15 methyl.

The group R'_1 and/or R'_2 in the form of a cyano can be converted to aminomethyl, from which a 3-cyano-2-methylisothioureidomethyl is prepared (according to C. Gordon et al., J. Org. Chem., 1970, 35(6), 2067-
20 2069) or a 2-cyanoguanidinomethyl is prepared (according to R.W. Turner, Synthesis, 1975, 332).

Step a1) is carried out in an inert solvent such as DMF, DMSO or THF, in a basic medium, for example in the presence of potassium hydroxide, a metal
25 alcoholate, a metal hydride, calcium carbonate or triethylamine.

Step b1) is carried out by heating under nitrogen in a solvent such as toluene, according to the method described by M.P. Cava et al., Tetrahedron,
30 1985, 41, 22, 5061.

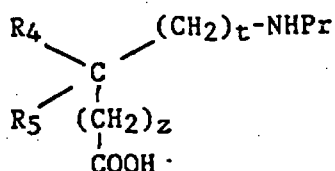
In the description below, the method comprising steps a1, b1 and c1 is referred to as method 1.

Alternatively, the compounds (I) can be prepared by another method, which is also a subject of the
35 present invention. Said method is characterized in that:



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a2) an amino acid of the formula

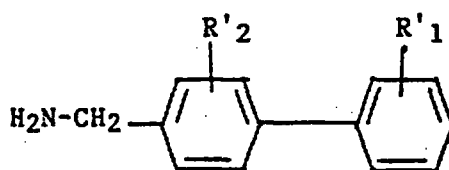


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in which z , t , R_4 and R_5 are as defined above for (I),
 and of which the amine group is protected by the Pr
 group, is reacted with a (biphenyl-4-yl)methylamine
 derivative of the formula

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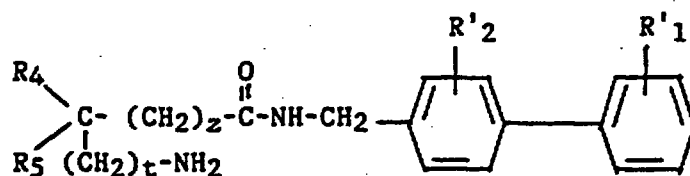
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in which R'_1 and R'_2 are respectively either R_1 and R_2
 or a precursor group of R_1 and R_2 ;

20

b2) after deprotection of the amine, the resul-
 ting compound of the formula



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25

is then treated with an alkyl ortho-ester of the
 formula $R_3C(OR)_3$ (10), in which R_3 is as defined above
 for (I) and R is a C_1 - C_4 alkyl;

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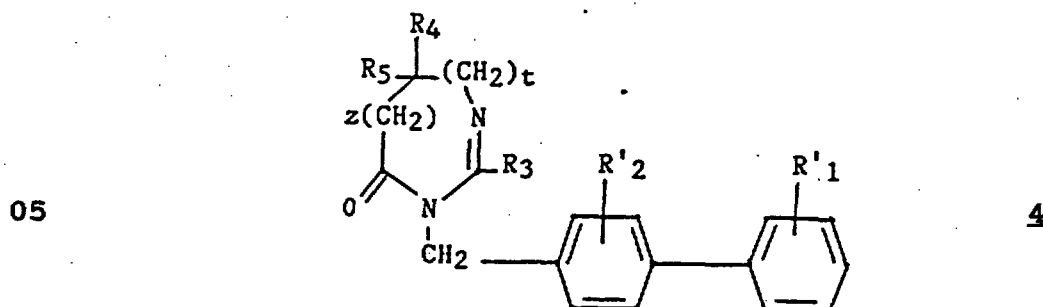
c2) if appropriate, the resulting compound of
 the formula

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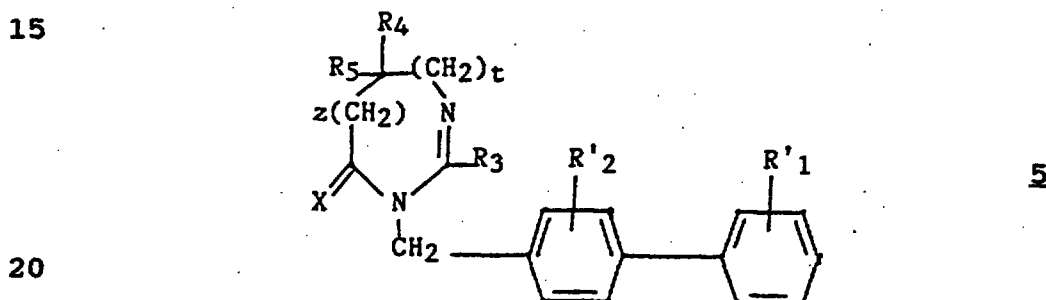


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10 is treated with Lawesson's reagent [2,4-bis(4-methoxy-phenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide]; and

d2) the compound thus obtained in b2 or c2, of the formula



is then treated under suitable conditions for preparing the compound (I) by conversion of the groups R'2 and/or R'1 to the groups R2 and/or R1 respectively.

25 The compounds 7 are known or are prepared by known methods (Chemistry of the Amino Acids, Greenstein and Winitz, published by John Wiley, 1961, vol. I, p. 697).

30 The compounds 8 are prepared according to European patent application 324 377. Step a2) is carried out under the usual conditions for the coupling of an acid with an amine, for example in the presence of BOP and DIPEA.

35 Step b2), which is the cyclization of the com-



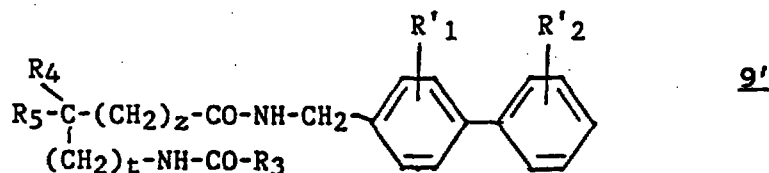
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pound 9 in the presence of 10, is carried out according to Jacquier et al. (Bull. Soc. Chim. France, 1971, (3), 1040-1051) and according to Brunken and Bach (Chem. Ber., 1956, 89, 1363-1373).

05 In the description below, the method comprising steps a2 to d2 is referred to as method 2.

In one variant of method 2, in step b2, it is possible, if appropriate, to isolate an intermediate 9' of the formula

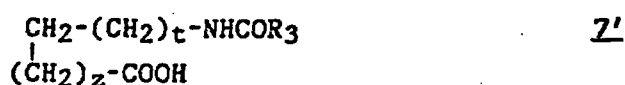
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and then to prepare the compound 4 by cyclization in an acid medium.

In another variant of method 2, in order to prepare a compound (I) in which R_4R_5 is a group $=\text{CR}_7\text{R}_8$,
20 an amino acid of the formula



25 can be reacted in an acid medium with an aldehyde or a ketone of the formula



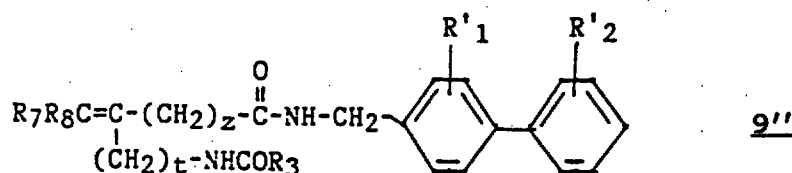
30 in which R_7 and R_8 are as defined above for (I), and the product is then reacted with the compound 8 to give a compound of the formula

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The cyclization of this compound in an acid medium leads to the compound 4.

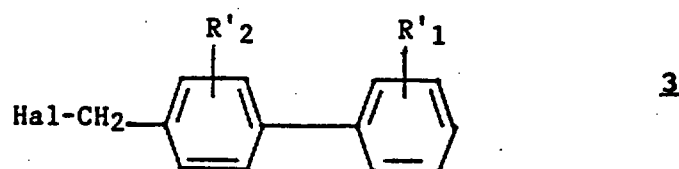
In this method, to prepare a compound (I) in which R_1 and/or R_2 are a carboxyl group, the substituents R'_1 and/or R'_2 are preferably a *tert*-butoxycarbonyl group.

Finally, another alternative for the preparation of the compounds (I) according to the invention in which z and t are equal to zero is the photooxidation method, which is also a subject of the present invention.

This last method is characterized in that

a3) a (biphenyl-4-yl)methyl derivative of the formula

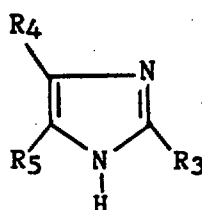
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25

in which Hal is a halogen atom and R'_1 and R'_2 are respectively either R_1 and R_2 or a precursor group of R_1 and R_2 , is reacted with an imidazole derivative of the formula

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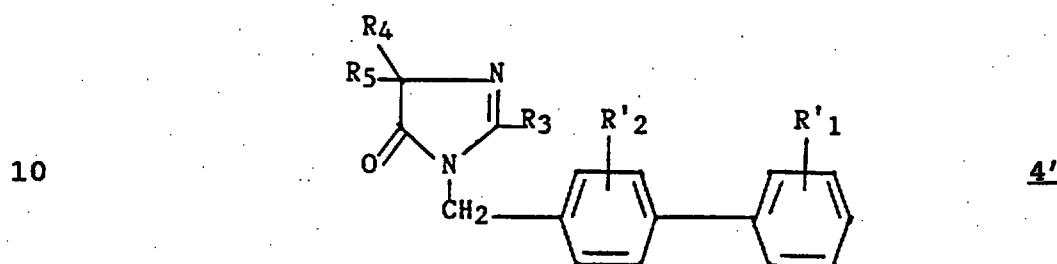
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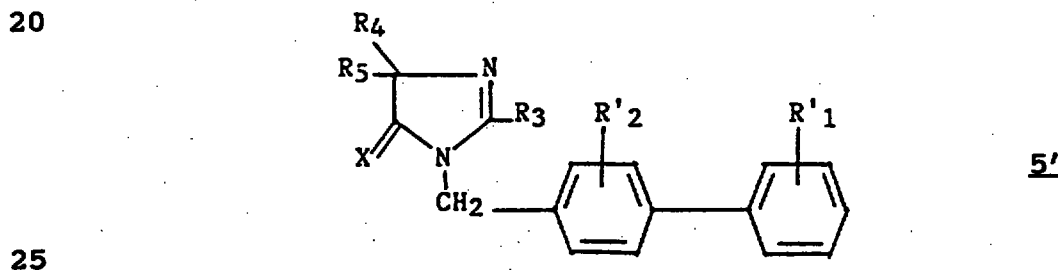
in which R_3 , R_4 and R_5 are as defined above for (I), in the presence of oxygen and UV irradiation and in a basic medium;

b3) if appropriate, the resulting compound of the formula



is treated with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide]; and

c3) the compound thus obtained in b3 or c3, of the formula



is then treated under suitable conditions for preparing the compound (I) by conversion of the groups R'_1 and/or R'_2 to the groups R_1 and/or R_2 respectively.

30 The imidazole derivative 11 is either commercially available, or known, or is prepared by known methods indicated above for the preparation of the compounds 2.

Step a3) is carried out in an inert solvent such as, for example, DMF; to facilitate the reaction,



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a photosensitizing product such as methylene blue can be added.

In the description below, the method comprising steps a3) to c3) is referred to as method 3.

05 The compounds (I) according to the invention in which R_4 and R_5 together are a group of the formula $(CH_2)_pY(CH_2)_q$ in which Y is an NH group can be prepared by catalytic hydrogenolysis of a corresponding compound (I) in which Y is a group $N-R_6$, R_6 being a benzyl.

10 The affinity of the products according to the invention for angiotensin II receptors was studied in a test for the binding of angiotensin II, labeled with iodine 125, to rat liver membrane receptors. The method used is the one described by S. KEPPENS et al.
15 in Biochem. J., 1982, 208, 809-817.

 The IC_{50} , namely the concentration which gives a 50% displacement of the labeled angiotensin II bound specifically to the receptor, is measured. The IC_{50} of the compounds according to the invention is less than
20 10^{-6} M.

 Also, the effect of the products according to the invention as angiotensin II antagonists was observed on different animal species in which the renin-angiotensin system had been activated beforehand (C.
25 LACOUR et al., J. Hypertension, 1989, 7 (suppl. 2), S33-S35).

 The compounds according to the invention are active after administration by different routes, especially after oral administration.

30 No signs of toxicity are observed with these compounds at the pharmacologically active doses.

 Thus the compounds according to the invention can be used in the treatment of various cardiovascular complaints, especially hypertension, heart failure and
35 venous insufficiency, as well as in the treatment of



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glaucoma, diabetic retinopathy and various complaints of the central nervous system, for example anxiety, depression, memory deficiencies or Alzheimer's disease.

05 The present invention further relates to pharmaceutical compositions containing an effective dose of a compound according to the invention, or of a pharmaceutically acceptable salt, and suitable excipients. Said excipients are chosen according to the pharmaceutical form and the desired mode of administration.

10 In the pharmaceutical compositions of the present invention for oral, sublingual, subcutaneous, intramuscular, intravenous, topical, intratracheal, intranasal, transdermal or rectal administration, the active principles of formula I above, or their salts if
15 appropriate, can be administered to animals and humans in unit forms of administration, mixed with conventional pharmaceutical carriers, for the prophylaxis or treatment of the above disorders or diseases. The appropriate unit forms of administration include forms
20 for oral administration, such as tablets, gelatin capsules, powders, granules and solutions or suspensions to be taken orally, forms for sublingual, buccal, intratracheal or intranasal administration, forms for subcutaneous, intramuscular or intravenous administration
25 and forms for rectal administration. For topical application, the compounds according to the invention can be used in creams, ointments or lotions.

To achieve the desired prophylactic or therapeutic effect, the dose of active principle can vary
30 between 0.01 and 50 mg per kg of body weight per day.

Each unit dose can contain from 0.1 to 1000 mg, preferably 1 to 500 mg, of active ingredients in combination with a pharmaceutical carrier. This unit dose can be administered 1 to 5 times a day so as to
35 administer a daily dosage of 0.5 to 5000 mg, preferably

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1 to 2500 mg.

When a solid composition in the form of tablets is prepared, the main active ingredient is mixed with a pharmaceutical vehicle such as gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets can be coated with sucrose, a cellulose derivative or other appropriate substances, or else they can be treated so as to have a prolonged or delayed activity and so as to release a predetermined amount of active principle continuously.

A preparation in the form of gelatin capsules is obtained by mixing the active ingredient with a diluent and pouring the resulting mixture into soft or hard gelatin capsules.

A preparation in the form of a syrup or elixir or for administration in the form of drops can contain the active ingredient in conjunction with a sweetener, which is preferably calorie-free, methylparaben and propylparaben as antiseptics, as well as a flavoring and an appropriate color.

The water-dispersible granules or powders can contain the active ingredient mixed with dispersants or wetting agents, or suspending agents such as polyvinylpyrrolidone, as well as with sweeteners or taste correctors.

Rectal administration is effected using suppositories prepared with binders which melt at the rectal temperature, for example cacao butter or polyethylene glycols.

Parenteral administration is effected using aqueous suspensions, isotonic saline solutions or sterile and injectable solutions which contain pharmacologically compatible dispersants and/or wetting agents, for example propylene glycol or butylene glycol.

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The active principle can also be formulated as microcapsules, with one or more carriers or additives if appropriate.

05 In addition to the products of formula I above or one of the pharmaceutically acceptable salts, the compositions of the present invention can contain other active principles such as, for example, tranquilizers or other drugs which can be useful in the treatment of the disorders or diseases indicated above.

10 Thus the present invention relates to pharmaceutical compositions containing several active principles in association, one being a compound according to the invention and it being possible for the other or others to be a beta-blocking compound, a calcium antagonist, a diuretic, a non-steroidal antiinflammatory or
15 a tranquilizer.

The following Examples illustrate the invention without however implying a limitation. The following abbreviations are used in these Examples: d denotes
20 density, RT denotes room temperature, $\text{KHSO}_4\text{-K}_2\text{SO}_4$ denotes an aqueous solution containing 16.6 g of potassium bisulfate and 33.3 g of potassium sulfate per liter.

The melting points (m.p.) are given in degrees
25 Celsius; unless indicated otherwise, they were measured without recrystallization of the product.

The purity of the products is checked by thin layer chromatography (TLC) or HPLC. The products are characterized by their NMR spectra run at 200 MHz in
30 deuterated DMSO with tetramethylsilane as the internal reference.

The following abbreviations are used in the interpretation of the NMR spectra:

s : singlet
35 sb : broad singlet

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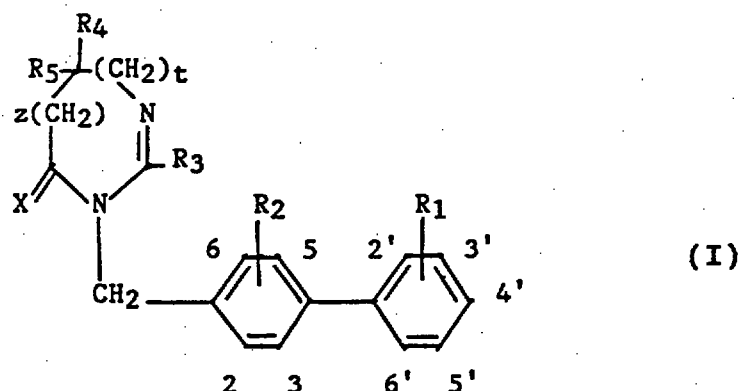


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d : doublet
t : triplet
q : quadruplet
quint : quintuplet
sext : sextuplet
m : unresolved signals or multiplet

In addition, im denotes imidazole.

Conventionally, the hydrogen atoms are numbered
on the biphenyl as shown in the following formula:



In the following compounds, z and t are zero
except where the compound prepared is a pyrimidinone.

EXAMPLE 1

2-n-Butyl-4-spirocyclopentane-1-[(2'-tert-butoxycarbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one
and 2-n-butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-one trifluoroacetate -
Method 2

A) 1-N-Fmoc-aminocyclopentanecarboxylic acid is prepared according to the method described by CHI-DEU CHANG et al. (Int. J. Peptide Protein Res., 1980, 15, 59-66). M.p. = 89-91°C.

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B) N-(2'-Tert-butoxycarbonylbiphenyl-4-ylmethyl)-1-(N-Fmoc-amino)cyclopentane-1-carboxamide

700 mg of the product prepared in the previous step are dissolved in 8 ml of DMF, and 576 mg of 4-aminomethyl-2'-tert-butoxycarbonylbiphenyl, 970 mg of BOP and a sufficient amount of DIPEA to bring the pH to 6 are added successively.

After stirring for 1 hour, the reaction medium is diluted with 100 ml of ethyl acetate and 20 ml of water; the organic phase is washed successively with a saturated solution of sodium bicarbonate, then with a KHSO_4 - K_2SO_4 solution and finally with a saturated solution of sodium chloride. After drying over sodium sulfate, the solution is evaporated to dryness to give an oil. $m = 1.2$ g.

C) N-(2'-Tert-butoxycarbonylbiphenyl-4-ylmethyl)-1-aminocyclopentane-1-carboxamide

The product obtained in the previous step is dissolved in 10 ml of DMF, 1 ml of diethylamine is then added and the mixture is stirred for 1 hour 15 minutes at RT. The reaction medium is taken up in 100 ml of ethyl acetate and 20 ml of water and the organic phase is then washed once with water and once with a saturated solution of sodium chloride and then dried over sodium sulfate and evaporated to dryness.

The residue is chromatographed on silica gel using an ethyl acetate/methanol/30% aqueous ammonia mixture (99/1/0.5; v/v/v) as the eluent to give 600 mg of the expected product.

- IR (CHCl_3):

3350 cm^{-1} : H (amide and amine)

1700 cm^{-1} : C=O (CO_2tBu)

1650 cm^{-1} : C=O (CONH)

- NMR spectrum:

1.25 ppm : s : 9 H : tBu

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2.15-1.40 ppm : m : 10 H : C_5H_8 , NH_2 4.40 ppm : d : 2 H : CH_2-NH

7.15-7.75 ppm : m : 8 H : biphenyl

8.60 ppm : t : 1 H : $NH-CH_2$

- 05 D) 2-n-Butyl-4-spirocyclopentane-1-[(2'-tert-butoxy-carbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one

394 mg of the product prepared in the previous step and 250 mg of ethyl orthovalerate are mixed in 2 ml of DCM. 1 drop of acetic acid is added and the mixture is then heated at 90°C with the DCM being allowed to evaporate off. After 1 hour 15 minutes, the reaction medium is taken up in 50 ml of ethyl acetate, 10 ml of water and 1 ml of a saturated solution of sodium bicarbonate. The organic phase is then washed with a saturated solution of sodium chloride and subsequently dried over sodium sulfate and evaporated to dryness. The residue is chromatographed on silica gel using an ethyl acetate/toluene mixture (1/2; v/v) as the eluent to give 390 mg of the expected product, which crystallizes. M.p. = 63-65°C.

10
15
20

- IR ($CHCl_3$):

1710-1720 cm^{-1} : C=O, C=O (ester and imidazoline)1625 cm^{-1} : C=N

- NMR spectrum:

25 0.88 ppm : t : 3 H : CH_3 (nBu)

1.20 ppm : s : 9 H : tBu

1.35 ppm : sext : 2 H : CH_3-CH_2- 1.58 ppm : quint : 2 H : $CH_3-CH_2-CH_2-$

1.95-1.65 ppm : m : 8 H : cyclopentane

30 2.42 ppm : t : 2 H : $CH_3-CH_2-CH_2-CH_2-$ 4.78 ppm : s : 2 H : $CH_2-C_6H_4-$

7.20-7.80 ppm : m : 8 H : aromatic protons

- Mass spectrum:

MH⁺ : 461

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E) 2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-one trifluoroacetate

180 mg of the product prepared in the previous step are treated with 3 ml of DCM and 4 ml of TFA for 45 minutes. After evaporation under vacuum, the residue is taken up in ether to give a white solid, which is filtered off, washed with ether and then dried under vacuum. m = 155 mg. M.p. = 176-178°C.

- NMR spectrum:

0.78 ppm : t : 3 H : CH₃ (nBu)
1.25 ppm : sext : 2 H : CH₃-CH₂
1.50 ppm : quint : 2 H : CH₃-CH₂-CH₂
1.75-2.00 : m : 8 H : cyclopentane
2.65 ppm : t : 2 H : CH₃-CH₂-CH₂-CH₂-
4.83 ppm : s : 2 H : CH₂-C₆H₄-
7.20-7.75 ppm : m : 8 H : aromatic protons

- Mass spectrum:

MH⁺ : 405

EXAMPLE 2

2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-one trifluoroacetate
- Method 1

A) 2-n-Butyl-4-spirocyclopentane-2-imidazolin-5-one

The ethyl ester of 1-aminocyclopentanecarboxylic acid is prepared according to ADKINS and BILLICA (J. Amer. Chem. Soc., 1948, 70, 3121).

Ethyl valerimide is prepared according to Mac ELVAIN (J. Amer. Chem. Soc., 1942, 64, 1825-1827) and then freed from its hydrochloride by reaction with potassium carbonate and extraction with DCM.

The ethyl ester of 1-aminocyclopentanecarboxylic acid (1.57 g) and ethyl valerimide (1.56 g) are dissolved in 12 ml of xylene containing 6 drops of acetic acid. After refluxing for 6 and a half hours,



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the reaction medium is concentrated under vacuum and the residue is then chromatographed on silica gel using a chloroform/methanol/acetic acid mixture (94/4/2; v/v/v) as the eluent. The fraction containing the expected product is evaporated several times in the presence of xylene and then benzene in order to remove the acetic acid. 1.91 g of product are obtained in the form of a thick oil.

- IR (CHCl_3):

1720 cm^{-1} : C=O

1635 cm^{-1} : C=N

Note: The fact that there is no visible band between 1500 and 1600 cm^{-1} indicates that, in chloroform solution, the product is an imidazolin-5-one.

- NMR spectrum:

0.92 ppm : t : 3 H : CH_3 (nBu)

1.35 ppm : sext : 2 H : $\text{CH}_3\text{-CH}_2\text{-}$

1.50-1.93 ppm : m : 10 H : $\text{CH}_3\text{-CH}_2\text{-CH}_2$ and cyclopentane

2.33 ppm : t : 2 H : $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-}$

10.7 ppm : m : NH

- Mass spectrum:

MH^+ : 195

The 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one prepared in step A can also be obtained by another procedure described below, using cyclopentanone as the starting material.

a) 1-Aminocyclopentanenitrile

This step is carried out according to A. Strecker (Org. Synth., 1955, 3).

1.97 g of sodium cyanide are dissolved in 3.9 ml of water in a round-bottomed flask and a solution containing 2.33 g of ammonium chloride in 5.9 ml of water and 3.5 ml of 20% aqueous ammonia is added; finally, 3 g of cyclopentanone in 3.8 ml of methanol

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are added to the flask. After stirring for 1 and a half hours, the mixture is heated at 60°C for 45 minutes, heating is then stopped, stirring is continued for 45 minutes and the mixture is then cooled to 25°C.

05 It is extracted several times with methylene chloride. The extracts are dried over sodium sulfate, filtered and concentrated under vacuum to give 4 g of the expected product in the form of an oil.

The 1-aminocyclopentanenitrile obtained is

10 dissolved in 300 ml of acetone, and a solution of 2.25 g of oxalic acid dihydrate in 200 ml of acetone is added, with stirring. The precipitate formed is filtered off, washed with acetone and then dried.

m = 4.71 g.

15 M.p. = 220°C.

This compound is 1-aminocyclopentanenitrile hemioxalate.

b) 1-Aminocyclopentaneacetamide

This step is carried out according to J.

20 Zabicky (The Chemistry of Amides, Interscience, New York, 1970, 119).

5.1 g of the oxalate obtained in the previous step are treated with 7.65 ml of concentrated sulfuric acid ($d = 1.84$) over 45 minutes, with stirring. The

25 evolution of a gas is observed and the temperature rises to 100°C. The mixture is cooled to about 35°C and poured into a mixture of ice and concentrated aqueous ammonia (10 g/2.8 ml). The suspension formed is extracted 6 times in succession with chloroform containing 5% of methanol. 3 ml of aqueous ammonia ($d =$

30 0.92) are added to the aqueous phase and the mixture is extracted again with chloroform containing methanol (1/0.5; v/v). The combined organic phases are dried over sodium sulfate, filtered and concentrated. The

35 expected product is obtained in the form of a white



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solid.

m = 3.79 g.

M.p. = 95°C.

The structure can be confirmed by the results
05 of analysis and the IR spectrum.

c) 2-n-Butyl-4-spirocyclopentane-2-imidazolin-
5-one

This step is carried out according to H.
Takenaka et al., Heterocycles, 1989, 29(6), 1185-89.

10 3 g of the compound prepared in the previous
step are placed in 70 ml of anhydrous THF and 3.3 ml of
triethylamine, and 3 ml of valeryl chloride in 10 ml of
anhydrous THF are added, with stirring. A white sus-
pension is formed. The intermediate which is formed,
15 but not isolated, is 1-(N-valeryl)aminocyclopentane-
carboxamide. 6 g of potassium hydroxide pellets, 7 ml
of water and 16 ml of methanol are added. The mixture
is refluxed for 2 and a half hours and 9 g of ammonium
chloride are then added. After stirring for 15 min-
utes, the mixture is concentrated under vacuum. The
20 residue obtained is taken up in 40 ml of water and
extracted with 10 ml of ethyl acetate and then twice
with 5 ml of ethyl acetate. The combined organic
phases are dried over sodium sulfate and filtered. The
25 filtrate is concentrated to dryness to give 4.85 g of
the expected product. The NMR spectrum is similar to
that described previously. The hydrochloride of this
compound can be prepared by the addition of concentra-
ted hydrochloric acid. The hydrochloride melts at
30 240°C with sublimation.

B) 2-n-Butyl-4-spirocyclopentane-1-[(2'-tert-butoxy-
carbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one

970 mg of the product obtained in step A) are
dissolved in 10 ml of DMF. 270 mg of sodium methylate
35 are added and the mixture is stirred for 15 minutes at

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RT. 2.08 g of 4-bromomethyl-2'-tert-butoxycarbonyl-biphenyl are added to the suspension and then, after 30 minutes, the mixture is heated at 40°C for 3 and a half hours under nitrogen. The reaction medium is taken up
05 in a mixture containing 100 ml of ethyl acetate, 10 ml of water and 1 ml of a saturated solution of sodium bicarbonate. The organic phase is washed with a saturated solution of sodium chloride and then dried over sodium sulfate and evaporated to dryness. The
10 residue is chromatographed on silica gel using an ethyl acetate/toluene mixture (1/2; v/v) as the eluent to give 1.25 g of the expected product, which crystallizes. M.p. = 63-66°C.

The IR and NMR spectra and the mass spectrum,
15 as well as the R_f, are identical to those obtained in step D) of Example 1.

C) 2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-one trifluoroacetate

1.22 g of the product obtained in the previous
20 step are stirred for 40 minutes in a solution containing 6 ml of DCM and 8 ml of TFA. After concentration under vacuum, the residue is taken up in ethyl ether; the white precipitate formed is filtered off, washed with ether and then dried under vacuum to give
25 1.15 g of the expected product. M.p. = 176-178°C.

The IR and NMR spectra and the mass spectrum are identical to those obtained in Example 1E; likewise, the R_f observed in TLC is identical.

30 EXAMPLE 3

2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-one trifluoroacetate
- Method 3

A) 2-n-Butylbenzimidazole is prepared according to W.O.
35 POOL (J. Amer. Chem. Soc., 1937, 59, 178) and 2-n-



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butyl-4,5,6,7-tetrahydrobenzimidazole is then prepared according to M. HARTMANN and L. PANIZZON (Helv. Chim. Acta, 1938, 21, 1692-1694). M.p. = 145°C.

- NMR spectrum:

- 05 0.82 ppm : t : 3 H : CH₃ (nBu)
 1.23 ppm : sext : 2 H : CH₃-CH₂-
 1.50 ppm : quint : 2 H : CH₃-CH₂-CH₂-
 1.65 ppm : s : 4 H : H₅, H₆ (tetrahydrobenzimidazole)
 2.35 ppm : s : 4 H : H₄, H₇ (tetrahydrobenzimidazole)
10 2.45 ppm : t : 2 H : CH₃-CH₂-CH₂-CH₂-
 11.1 ppm : m : NH

- Mass spectrum:

M⁺ : 178

- 15 B) 2-n-Butyl-4-spirocyclopentane-1-[(2'-tert-butoxy-carbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one

- 1 g of the product prepared in the previous step is dissolved in 45 ml of DMF with 303 mg of sodium methylate and a few mg of methylene blue. Oxygen is bubbled into the reaction medium, which is illuminated
20 with a UV lamp. After 15 minutes, 2.14 g of 4-bromo-methyl-2'-tert-butoxycarbonylbiphenyl are added and then, after 1 hour, the reaction medium is taken up in 300 ml of ethyl acetate to which 50 ml of water and 5 ml of a saturated solution of sodium bicarbonate have
25 been added. The organic phase is then washed with a saturated solution of sodium chloride and subsequently dried over sodium sulfate and evaporated to dryness. The residue is chromatographed on silica gel using an ethyl acetate/toluene mixture (1/2; v/v) as the eluent
30 to give 610 mg of the expected product, which crystallizes. M.p. = 62-65°C.

 The IR and NMR spectra and the mass spectrum, as well as the R_f, are identical to those obtained previously for the same compound.

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C) 2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-one trifluoroacetate

05 This compound is obtained by treatment in an acid medium as described in the last step of Example 1 and Example 2. The physicochemical data are identical to those obtained for the same compound prepared by method 1 or 2.

EXAMPLE 4

10 2-n-Butyl-4,4-dimethyl-1-[(2'-tert-butoxy-carbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one and 2-n-butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4,4-dimethyl-2-imidazolin-5-one trifluoroacetate - Method 1

A) 2-n-Butyl-4,4-dimethyl-2-imidazolin-5-one

15 The ethyl ester of alpha-aminoisobutyric acid is prepared according to R. Jacquier et al. (Bull. Soc. Chim. France, 1971, (3), 1040-1051). 650 mg of this compound and 780 mg of ethyl valerimidate are dissolved in 8 ml of xylene containing 4 drops of acetic acid and
20 the solution is refluxed for 7 hours. The reaction medium is then concentrated under vacuum and the residue is chromatographed on silica gel using a chloroform/methanol/acetic acid mixture (95/5/2; v/v/v) as the eluent. After several evaporations with xylene and
25 then benzene to remove the acetic acid, 560 mg of the expected product are obtained, which crystallizes. M.p. = 35-38°C.

- IR (CHCl₃):

1725 cm⁻¹ : C=O

30 1635 cm⁻¹ : C=N

Note: The absence of a signal between 1500 and 1600 cm⁻¹ confirms that the compound present in chloroform solution is a 2-imidazolin-5-one.

- NMR spectrum:

35 0.92 ppm : t : 3 H : CH₃ (nBu)

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- 1.20 ppm : s : 6 H : $C(CH_3)_2$
1.38 ppm : sext : 2 H : CH_3-CH_2
1.63 ppm : quint : 2 H : $CH_3-CH_2-CH_2-$
2.38 ppm : t : 2 H : $CH_3-CH_2-CH_2-CH_2-$
05 10.7 ppm : m : 1 H : N-H
- Mass spectrum:
MH⁺ : 169
- B) 2-n-Butyl-4,4-dimethyl-1-[(2'-tert-butoxycarbonyl-biphenyl-4-yl)methyl]-2-imidazolin-5-one
- 10 520 mg of the product prepared in the previous step are dissolved in 10 ml of DMF. 167 mg of sodium methylate are added and the mixture is stirred under nitrogen for 15 minutes. 1.25 g of 4-bromomethyl-2'-tert-butoxycarbonylbiphenyl are then added and the mixture is stirred at 40°C for 3 and a half hours. The reaction medium is taken up in 150 ml of ethyl acetate and then 20 ml of water and 2 ml of a saturated solution of sodium bicarbonate. The organic phase is washed with a saturated solution of sodium chloride, dried over sodium sulfate and evaporated to dryness. The residue is chromatographed on silica gel using an ethyl acetate/toluene mixture (1.2/2; v/v) as the eluent to give 570 mg of the expected product, which crystallizes. M.p. = 98-100°C.
- 15 20
- 25 - IR ($CHCl_3$):
1710-1720 cm^{-1} : C=O, C=O (imidazolinone, ester)
1625 cm^{-1} : C=N
- NMR spectrum:
0.78 ppm : t : 3 H : CH_3 (nBu)
30 1.08 ppm : s : 9 H : $C(CH_3)_3$
1.15 ppm : s : $C(CH_3)_2$ }
1.20 ppm : sext : CH_3-CH_2- } 8 H
1.45 ppm : quint : 2 H : $CH_3-CH_2-CH_2-$
2.30 ppm : t : 2 H : $CH_3-CH_2-CH_2-CH_2-$
35 4.65 ppm : s : 2 H : $CH_2-C_6H_4-$



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7.15-7.65 ppm : m : 8 H : aromatic protons

An NOE (Nuclear Overhauser Effect) study confirms the position of the 5-one and 4,4-dimethyl substituents on the imidazolinone.

05 - Mass spectrum:

MH⁺ : 435

C) 2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4,4-dimethyl-2-imidazolin-5-one trifluoroacetate

10 460 mg of the product prepared in the previous step are treated with 3 ml of DCM and 4 ml of TFA for 45 minutes. After concentration under vacuum, the residue is taken up in ether and the precipitate formed is filtered off, washed with ether and then dried under vacuum to give 450 mg of the expected product in the
15 form of a white solid. M.p. = 168-171°C.

- NMR spectrum:

0.82 ppm : t : 3 H : CH₃ (nBu)

1.30 ppm : sext : CH₃-CH₂-

1.35 ppm : s : C(CH₃)₂- } 8 H

20 1.55 ppm : quint : 2 H : CH₃-CH₂-CH₂-

2.62 ppm : t : 2 H : CH₃-CH₂-CH₂-CH₂-

4.82 ppm : s : 2 H : CH₂-C₆H₄-

7.20-7.75 : m : 8 aromatic H

- Mass spectrum:

25 MH⁺ : 379

EXAMPLE 5

1-[(2'-Cyanobiphenyl-4-yl)methyl]-2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one and 2-n-butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)-
30 methyl]-2-imidazolin-5-one - Method 1

A) 1-[(2'-Cyanobiphenyl-4-yl)methyl]-2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one

35 A mixture containing 250 mg of sodium hydride (as an 80% dispersion in mineral oil) and 5 ml of DMF

This Sheet Has Been Replaced



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is prepared under a nitrogen atmosphere and a solution containing 0.97 g of 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one (prepared in Example 2, step A) in 10 ml of DMF is added dropwise. The mixture is stirred
05 for 30 minutes at RT and a solution of 1.5 g of 4-bromomethyl-2'-cyanobiphenyl in 10 ml of DMF is then added. After stirring for 1 hour at RT, the DMF is evaporated off under reduced pressure, the residue is then taken up with ethyl acetate and the organic phase
10 is washed with water and then dried over sodium sulfate, filtered and evaporated. The residue is chromatographed on silica gel using a DCM/ethyl acetate mixture (9/1; v/v) as the eluent. 1.68 g of the expected product are recovered. M.p. = 92-93°C.

15 B) 2-n-Butyl-4-spirocyclopentane-1-[(2'-(triphenylmethyl)tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one

1.56 g of the previous product, 2.6 g of tributyltin azide and 30 ml of xylene are refluxed for 66
20 hours. The xylene is then evaporated off and the residue is dissolved in 20 ml of DCM and 5 ml of THF with the addition of 0.8 ml of 10 N sodium hydroxide solution and, after stirring for 30 minutes, 2.5 g of triethyl chloride, and the mixture is stirred for 26 hours.
25 After evaporation of the solvents, the residue is taken up in ethyl acetate and washed with water by means of a 3% solution of potassium bisulfate and water. It is dried and evaporated. The residue is chromatographed on alumina using a hexane/ethyl acetate mixture (9/1;
30 v/v) as the eluent to give 1.97 g of the expected product. M.p. = 150-152°C.

C) 2-n-Butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one

1.96 g of the product prepared in the previous
35 step are dissolved in 10 ml of methanol and 10 ml of

THF. After the reaction medium has been cooled to 5°C, 1.5 ml of 4 N hydrochloric acid are added and the mixture is stirred for 3 hours at RT and 1 hour at 30°C. After evaporation of the solvents, the residue is taken up in water and the pH is brought to 12 by the addition of 10 N sodium hydroxide solution. The aqueous phase is extracted with ether, toluene and ether again. The aqueous phase is acidified to pH 2 by the addition of 1 N hydrochloric acid and then extracted with ethyl acetate and the extract is dried and evaporated. The white solid obtained is dried at 50°C under 0.05 mm of mercury to give 840 mg of the expected product. M.p. = 180-181°C.

- NMR spectrum:

- 0.75 ppm : t : 3 H : CH₃ (nBu)
1.10 ppm : sext : 2 H : CH₃-CH₂-
1.20 ppm : quint : 2 H : CH₃-CH₂-CH₂-
1.5-2 ppm : m : 8 H : -C₅H₈
2.2 ppm : t : 2 H : CH₃-CH₂-CH₂-CH₂-
4.6 ppm : s : 2 H : CH₂-C₆H₄-
7 ppm : s : 4 H : CH₂-C₆H₄-
7.35-7.7 ppm : m : 4 H : aromatic H_{3',4',5',6'}

An NOE study confirms the position of the 5-one substituent on the imidazole.

- D) Potassium salt of 2-n-butyl-4-spirocyclopentane-1-[(2'-(tetrazol-5-yl)biphenyl-4-yl)methyl]-2-imidazolin-5-one

970 mg of the compound obtained in the previous step are dissolved in 40 ml of an isopropanol/methanol mixture (1/1; v/v) and the pH is adjusted to 12 by the addition of an 85% solution of potassium hydroxide in a methanol/water mixture (20/1; v/v). The reaction medium is evaporated, the residue is taken up in isopropanol and the medium is evaporated again. The residue is dissolved in 20 ml of isopropanol, with gentle

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heating, and then left to return to room temperature. The mixture is left to decant, the filtrate is evaporated and the residue is then taken up in heptane. After trituration, the product solidifies; it is filtered off
05 and then washed again with heptane and dried under vacuum to give 945 mg of the expected potassium salt. M.p. = 142-144°C.

- Elemental analysis: $C_{25}H_{27}KN_6O.H_2O$

	calc. %	C : 61.95	H : 6.03	N : 17.34
10	found %	62.02	6.13	17.14

EXAMPLE 6

2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-
4-(4-spirotetrahydropyran)-2-imidazolin-5-one tri-
15 fluoroacetate and 2-n-butyl-4-(4-spirotetrahydropyran)-
1-[(2'-tert-butoxycarbonylbiphenyl-4-yl)methyl]-2-
imidazolin-5-one - Method 2

A) 4-Aminotetrahydropyran-4-carboxylic acid is prepared from tetrahydropyran-4-one by the method described in
20 German patent 2 215 721.

B) 4-(N-Benzyloxycarbonylamino)-4-carboxytetrahydro-
pyran

1.015 g of the compound of step A are placed in 12 ml of water and treated at 10°C with 1.22 ml of di-
25 isopropylethylamine and then 3.33 g of N-(benzyloxy-carbonyloxy)succinimide dissolved in 12 ml of acetonitrile. After 1 hour 15 minutes, the reaction medium is diluted with 70 ml of ethyl acetate and 10 ml of water and the pH is brought to 2 with a saturated
30 solution of potassium bisulfate.

After decantation, the organic phase is washed with a saturated solution of sodium chloride, dried over sodium sulfate and then evaporated under vacuum. The residue is diluted with 60 ml of ether, after which
35 7 mmol of dicyclohexylamine are added. The precipitate



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formed is filtered off and washed with ether; it is then dissolved in an ethyl acetate/water mixture and the pH is brought to 1.5 with a saturated solution of potassium bisulfate. The organic phase is decanted, washed with a saturated solution of sodium chloride and evaporated under vacuum to give 1.9 g of a white solid. M.p. = 110-115°C.

C) N-(2'-Tert-butoxycarbonylbiphenyl-4-ylmethyl)-4-(N-benzyloxycarbonylamino)tetrahydropyran-4-carboxamide

850 mg of the compound prepared in step B are dissolved in 15 ml of DMF, and equimolar amounts of 4-aminomethyl-2'-tert-butoxycarbonylbiphenyl, DIPEA and then BOP (10% excess) are added. After 40 minutes, the medium is taken up in 200 ml of ethyl acetate and 200 ml of water. The organic phase is decanted and then washed twice with a saturated solution of sodium bicarbonate, twice with a 5% solution of sodium bisulfate and then once with a saturated solution of sodium chloride. After drying over sodium sulfate, the organic phase is evaporated under vacuum to give 1.8 g of the expected product.

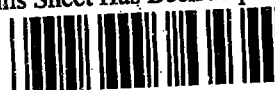
D) N-(2'-Tert-butoxycarbonylbiphenyl-4-ylmethyl)-4-aminotetrahydropyran-4-carboxamide

The product obtained in step C is dissolved in 30 ml of methanol. 400 mg of 10% palladium-on-charcoal are added and the mixture is hydrogenated at atmospheric pressure. After 1 hour, the catalyst is filtered off and the filtrate is then concentrated under vacuum. The residue is chromatographed on silica using an ethyl acetate/methanol/33% aqueous ammonia mixture (99/1/0.5; v/v/v) as the eluent to give 0.93 g of the expected product in the form of a white solid. M.p. = 125-127°C.

- NMR spectrum:

8.50 ppm : t : 1 H : amide H

This Sheet Has Been Replaced



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7.60-7.05 ppm : m : 8 H : aromatic protons

4.25 ppm : d : 2 H : $\text{CH}_2\text{-C}_6\text{H}_4\text{-}$

3.70-3.50 ppm : m : 4 H : CH_2 in the 2 and 6 positions of the tetrahydropyran

05

2.00-1.80 ppm : m : 4 H : CH_2 in the 3 and 5 positions of the tetrahydropyran

1.05 ppm : s : 9 H : tBu

10 E) 2-n-Butyl-4-(4-spirotetrahydropyran)-1-[(2'-tert-butoxycarbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one

A mixture containing 0.9 g of the compound obtained in step D, 327 mg of methyl orthovalerate and 2 drops of acetic acid is heated for 3 hours at 110°C.

15 The reaction medium is taken up in 100 ml of ethyl acetate, then washed with a saturated solution of sodium bicarbonate and a saturated solution of sodium chloride and then dried over sodium sulfate and the ethyl acetate is evaporated off. The residue obtained

20 is chromatographed on silica using an ethyl acetate/toluene mixture (2/1; v/v) as the eluent to give 550 mg of the expected product in the form of a wax.

- NMR spectrum:

7.05-7.60 ppm : m : 8 H : aromatic protons

25 4.63 ppm : s : 2 H : $\text{CH}_2\text{-C}_6\text{H}_4\text{-}$

3.85-3.55 ppm : m : 4 H : CH_2 in the 2 and 6 positions of the tetrahydropyran

2.30 ppm : t : 2 H : $\text{CH}_2\text{-C}_3\text{H}_7$

30 1.05-1.80 ppm : m : 8 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$ and CH_2 in the 3 and 5 positions of the tetrahydropyran

1.03 ppm : s : 9 H : tBu

0.75 ppm : t : 3 H : $(\text{CH}_2)_3\text{-CH}_3$

35

This Sheet Has Been Replaced



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- IR (CHCl_3):

1710-1720 cm^{-1} : C=O, C=O

1625 cm^{-1} : C=N

05 F) 2-n-Butyl-4-(4-spirotetrahydropyran)-1-[(2'-tert-butoxycarbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one

530 mg of the product obtained in the previous step are treated with 4 ml of dichloromethane and 5 ml of TFA for 45 minutes. After evaporation under vacuum, 10 the residue is taken up in ether and the precipitate formed is filtered off, washed with ether and then dried under vacuum to give 510 mg of the expected product. M.p. = 159-162°C.

- NMR spectrum:

15 7.80-7.10 ppm : m : 8 H : aromatic protons

4.80 ppm : s : 2 H : $\text{CH}_2\text{-C}_6\text{H}_4\text{-}$

4.00-3.75 ppm : m : 4 H : CH_2 in the 2 and 6 positions of the tetrahydropyran

20 2.60 ppm : t : 2 H : $\text{CH}_2\text{-C}_3\text{H}_7$

1.45-2.00 ppm : m : 6 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$ and CH_2 in the 3 and 5 positions of the tetrahydropyran

1.30 ppm : sext : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

25 0.80 ppm : t : 3 H : $(\text{CH}_2)_3\text{-CH}_3$

EXAMPLE 7

2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-[spiro(1-benzyl-4-piperidine)]-2-imidazolin-5-one trifluoroacetate and 2-n-butyl-4-[spiro(1-benzyl-4-piperidine)]-1-[(2'-tert-butoxycarbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one - Method 1

30 A) 4-Amino-1-benzylpiperidine-4-carboxylic acid is prepared from N-benzylpiperidin-4-one by the method described in German patent 2 215 721.



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B) Ethyl 4-amino-1-benzylpiperidine-4-carboxylate

3.80 g of the compound prepared in step A are added to a solution of 13 g of hydrochloric acid in 50 ml of ethanol at 0°C and the mixture is then refluxed for 5 hours. After concentration under vacuum, the residue is washed with ether and then dissolved in an ether/water mixture, to which a saturated solution of potassium carbonate is added to bring the pH to 9. The ether phase is decanted, washed with a saturated solution of sodium chloride, dried over sodium sulfate and then evaporated to dryness to give 3.50 g of the expected product in the form of an oil.

- NMR spectrum:

7.20-7.40 ppm : m : 5 H : aromatic protons
4.10 ppm : q : 2 H : CH₂-CH₃
3.45 ppm : s : 2 H : CH₂ of the benzyl
2.25-2.60 ppm : m : 4 H : CH₂ in the 2 and 6 positions of the piperidine
1.80-2.05 ppm : m : 2 H } CH₂ in the 3 and 5 positions of the piperidine
1.20-1.40 ppm : m : 2 H }
1.12 ppm : t : 3 H : CH₃-CH₂-

C) 2-n-Butyl-4-[spiro(1-benzyl-4-piperidine)]-2-imidazolin-5-one

Ethyl valerimide is prepared as in Example 2, step A. 2.06 g of ethyl valerimide, 3.40 g of the compound prepared in step B and 8 drops of acetic acid are mixed in 15 ml of xylene and the mixture is refluxed for 6 hours. After concentration under vacuum, the residue is chromatographed on silica gel using a chloroform/methanol/acetic acid mixture (82/15/3; v/v/v) as the eluent. 2.80 g of the expected product are obtained after extraction with chloroform at pH 9 to remove the acetic acid. M.p. = 170-172°C.

- IR (chloroform):

1725 cm⁻¹ : C=O

This Sheet Has Been Replaced



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1640 cm^{-1} : C=N

- NMR spectrum:

7.10-7.30 ppm : m : 5 H : aromatic protons

3.45 ppm : s : 2 H : $-\text{CH}_2-\text{C}_6\text{H}_5$

05 1.10-2.75 ppm : 5 m : 14 H : CH_2 in the 2, 3, 5 and
6 positions of the
piperidine and
 $(\text{CH}_2)_3-\text{CH}_3$

0.80 ppm : t : 3 H : $(\text{CH}_2)_3-\text{CH}_3$

10 D) 2-n-Butyl-4-[spiro(1-benzyl-4-piperidine)]-1-[(2'-
tert-butoxycarbonylbiphenyl-4-yl)methyl]-2-imidazolin-
5-one

513 mg of sodium methylate and, after 15
minutes, 4.16 g of 4-bromomethyl-2'-tert-butoxycar-
15 bonylbiphenyl are added to a solution of 2.78 g of the
compound obtained in step C in 25 ml of DMF. The reac-
tion medium is heated at 40°C for 5 hours and then
taken up in 300 ml of ethyl acetate, 50 ml of water and
5 ml of a saturated solution of sodium bicarbonate.
20 The organic phase is decanted, washed once more with a
saturated solution of sodium chloride, dried over
sodium sulfate and evaporated under vacuum. The resi-
due is chromatographed on silica using an ethyl ace-
tate/methanol mixture (95/5; v/v) as the eluent to give
25 0.98 g of the expected product. M.p. = 103-106°C.

- IR (CHCl_3):1710-1725 cm^{-1} : C=O, C=O (imidazoline, ester)1630 cm^{-1} : C=N

- NMR spectrum:

30 7.70-7.10 ppm : m : 13 H : aromatic protons

4.70 ppm : s : 2 H : $\text{CH}_2-\text{C}_6\text{H}_4-$ 3.55 ppm : s : 2 H : $\text{CH}_2-\text{C}_6\text{H}_5$

1.20-2.75 ppm : 5 m : 14 H : CH_2 in the 2, 3, 5 and 6
positions of the piperi-
dine and $(\text{CH}_2)_3-\text{CH}_3$

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This Sheet Has Been Replaced



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1.15 ppm : s : 9 H : tBu

0.85 ppm : t : 3 H : (CH₂)₃-CH₃

05 E) 2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-
[spiro(1-benzyl-4-piperidine)]-2-imidazolin-5-one
trifluoroacetate

10 350 mg of the compound obtained in step D are
dissolved in 4 ml of dichloromethane and 5 ml of TFA.
After 45 minutes, the medium is concentrated under
vacuum, the residue is then taken up in an ether/
hexane mixture and the precipitate formed is filtered
off, washed with ether and dried under vacuum to give
350 mg of the expected product. M.p. = 198-200°C.

- NMR spectrum:

15 7.05-7.75 ppm : m : 13 H : aromatic protons
4.75 ppm : s : 2 H : CH₂-C₆H₄-
4.40 ppm : s : 2 H : CH₂-C₆H₅
3.20-3.60 ppm : m : 4 H : CH₂ in the 2 and 6 posi-
tions of the piperidine
2.35 ppm : t : 2 H : CH₂-CH₂-CH₂-CH₃
20 2.20-1.40 ppm : 3 unresolved signals : CH₂ in the 3
and 5 posi-
tions of the
piperidine and
CH₂-CH₂-CH₂-
25 CH₃
1.25 ppm : sext : 2 H : CH₂-CH₂-CH₂-CH₃
0.80 ppm : t : 3 H : (CH₂)₃-CH₃

EXAMPLE 8

30 2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-
4-(4-spiropiperidine)-2-imidazolin-5-one ditrifluoro-
acetate and 2-butyl-4-(4-spiropiperidine)-1-[(2'-tert-
butoxycarbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one

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This Sheet Has Been Replaced



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A) 2-n-Butyl-4-(4-spiropiperidine)-1-[(2'-tert-butoxy-carbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one

300 mg of the compound of Example 7, step D, are dissolved in 10 ml of methanol. 180 mg of 10% palladium-on-charcoal are added and the mixture is hydrogenated for 3 hours at atmospheric pressure. The catalyst is filtered off and the filtrate is concentrated under vacuum to give 200 mg of the expected product.

10 - NMR spectrum:

7.20-7.75 ppm : m : 8 H : aromatic protons

4.75 ppm : s : 2 H : $\text{CH}_2\text{-C}_6\text{H}_4\text{-}$

3.00-1.70 ppm : 3 unresolved signals for the 4 CH_2 of the piperidine

15 2.40 ppm : t : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

1.60 ppm : quint : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

1.35 ppm : sext : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

1.20 ppm : s : 9 H : tBu

0.90 ppm : t : 3 H : $(\text{CH}_2)_3\text{-CH}_3$

20 B) 2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-(4-spiropiperidine)-2-imidazolin-5-one ditrifluoroacetate

160 mg of the product obtained in step A are stirred for 45 minutes in 3 ml of dichloromethane and 4 ml of trifluoroacetic acid. The mixture is concentrated under vacuum and the residue is taken up in ether to give a gum and then a foam after drying under vacuum (150 mg). M.p. = 80-85°C.

- NMR spectrum:

7.15-7.80 ppm : m : 8 H : aromatic protons

30 4.75 ppm : s : 2 H : $\text{CH}_2\text{-C}_6\text{H}_4\text{-}$

3.20-1.60 ppm : 3 unresolved signals : 4 CH_2 of the piperidine

2.40 ppm : t : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

1.50 ppm : quint : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

35 1.30 ppm : sext : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$



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0.80 ppm : t : 3 H : $(\text{CH}_2)_3\text{-CH}_3$

EXAMPLE 9

05 2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-
4,4-diphenyl-2-imidazolin-5-one trifluoroacetate and 2-
n-butyl-4,4-diphenyl-1-[(2'-tert-butoxycarbonylbi-
phenyl-4-yl)methyl]-2-imidazolin-5-one - Method 1

A) Valeramide hydrochloride

10 6 g of ethyl valerimide hydrochloride are
added to a solution of 6.75 g of ammonia in 80 ml of
methanol at 0°C. After 18 h, the reaction medium is
concentrated under vacuum to give the expected product
in the form of a white solid.

B) 2-n-Butyl-4,4-diphenyl-2-imidazolin-5-one

15 This compound is prepared according to the pro-
cedure described by J. NYITRAI and K. LEMPert in Tetra-
hedron, 1969, 25, 4265-4275, from benzil and valerami-
dine hydrochloride. M.p. = 135°C.

- IR (CHCl_3):20 1725 cm^{-1} : C=O1640 cm^{-1} : C=N

- NMR spectrum:

7.20-7.50 ppm : m : 10 H : aromatic protons

2.50 ppm : t : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$ 25 1.65 ppm : quint : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$ 1.35 ppm : sext : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$ 0.90 ppm : t : 3 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

11 ppm : sb : NH

30 C) 2-n-Butyl-4,4-diphenyl-1-[(2'-tert-butoxycarbonylbi-
phenyl-4-yl)methyl]-2-imidazolin-5-one

This compound is prepared according to the
usual method by reacting 4-bromomethyl-2'-tert-butoxy-
carbonylbiphenyl with the compound prepared in step B,
in the presence of sodium methylate in DMF.

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This Sheet Has Been Replaced



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- IR (CHCl_3):

1715-1725 cm^{-1} : C=O, C=O (ester, imidazolinone)

1635 cm^{-1} : C=N

- NMR spectrum:

05 7.25-7.80 ppm : m : 18 H : aromatic protons

4.85 ppm : s : 2 H : $\text{N-CH}_2\text{-C}_6\text{H}_4\text{-}$

2.60 ppm : t : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

1.75 ppm : quint : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

1.40 ppm : sext : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

10 1.15 ppm : s : 9 H : tBu

0.90 ppm : t : 3 H : CH_3 of the n-butyl

D) 2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4,4-diphenyl-2-imidazolin-5-one trifluoroacetate

500 mg of the product prepared in step C are
15 treated with 2.5 ml of dichloromethane and 2.5 ml of trifluoroacetic acid at 20°C for 40 minutes. After concentration under vacuum, the residue is taken up in an ether/hexane mixture and the precipitate formed is filtered off, washed with hexane and dried to give 440
20 mg of the expected product. M.p. = 55-60°C.

- NMR spectrum:

7.15-7.80 ppm : m : 18 H : aromatic protons

4.85 ppm : s : 2 H : $\text{N-CH}_2\text{-C}_6\text{H}_4\text{-}$

2.60 ppm : t : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

25 1.70 ppm : quint : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

1.40 ppm : sext : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$

0.90 ppm : t : 3 H : CH_3 of the butyl

EXAMPLE 10

30 2-n-Butyl-3-[(2'-carboxybiphenyl-4-yl)methyl]-6-spirocyclopentane-5,6-dihydro-1H-pyrimidin-4-one trifluoroacetate

A) (1-Aminocyclopentyl)acetic acid

Cyclopentylideneacetic acid is prepared according to G.A.R. KON and R.P. LINSTEAD, J. Chem. Soc.,
35

This Sheet Has Been Replaced



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1925, 127, 616. 740 mg of this acid and 5 ml of 20% aqueous ammonia are placed in an autoclave and the mixture is heated at 150°C for 24 hours. After evaporation of the solvents, the residue is chromatographed on
05 a silica column using a DCM/methanol/20% aqueous ammonia solution mixture (70/30/1; v/v/v) as the eluent to give 330 mg of the expected acid.

B) Ethyl (1-aminocyclopentyl)acetate

330 mg of the acid are dissolved in 10 ml of
10 ethanol. The solution is cooled in an ice bath and saturated with gaseous hydrochloric acid. After 24 hours under reflux, the reaction medium is evaporated, the residue is taken up in a solution of sodium carbonate and extracted with ethyl acetate and the extract
15 is then dried over sodium sulfate, filtered and evaporated to give 312 mg of the expected ester.

C) 2-n-Butyl-6-spirocyclopentane-5,6-dihydro-1H-pyrimidin-4-one

A mixture containing 310 mg of the compound
20 obtained in step B, 348 mg of ethyl valerimide, 10 ml of xylene and 6 drops of acetic acid is brought to the reflux point. After 2 hours and 18 hours, a further 348 mg of ethyl valerimide are added and, after a total reflux time of 24 hours, the reaction medium is
25 evaporated and then chromatographed on silica using a DCM/methanol mixture (97/3; v/v) as the eluent to give 153 mg of the expected product.

D) 2-n-Butyl-3-[(2'-tert-butoxycarbonylbiphenyl-4-yl)-methyl]-5,6-dihydro-1H-pyrimidin-4-one

30 A mixture of 10 ml of DMF and 40 mg of sodium hydride as an 80% dispersion in oil is prepared under a nitrogen atmosphere. 144 mg of the compound prepared in step C, dissolved in 5 ml of DMF, are added dropwise at room temperature. After stirring for 30 minutes, a
35 solution of 288 mg of 4-bromomethyl-2'-tert-butoxy-

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carbonylbiphenyl in 5 ml of DMF is added. The mixture is stirred for 2 hours and then evaporated and the residue is taken up in water and extracted with ethyl acetate. The extract is dried over sodium sulfate, filtered, evaporated and then purified by column chromatography using a hexane/ethyl acetate mixture (85/5; v/v) as the eluent to give 174 mg of the expected product.

E)

10 ml of trifluoroacetic acid are cooled in a bath of iced water and 161 mg of the compound prepared in step D are added. The mixture is stirred for 30 minutes and then evaporated. The residue is taken up in ethyl ether and the mixture is then evaporated again. This operation is repeated and the residue is then dried under vacuum to give 140 mg of the expected compound in the form of an amorphous powder. M.p. = 108-115°C.

- NMR spectrum:

0.9 ppm : t : 3 H : $(\text{CH}_2)_3\text{-CH}_3$
1.1 to 2.1 ppm : m : 12 H : cyclopentane and $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$
2.7 ppm : t : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$
3.1 ppm : s : 2 H : $\text{-CH}_2\text{-CO}$
5.1 ppm : s : 2 H : $\text{N-CH}_2\text{-C}_6\text{H}_5$
7.2 to 7.8 ppm : m : 8 H : aromatic protons

EXAMPLE 11

2-n-Butyl-4-spirocyclopentane-1-[(2'-tert-butoxycarbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-thione and 2-n-butyl-1-[(2'-carboxybiphenyl-4-yl)-methyl]-4-spirocyclopentane-2-imidazolin-5-thione trifluoroacetate

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- 50 -

A) 2-n-Butyl-4-spirocyclopentane-1-[(2'-tert-butoxy-carbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-thione

5.63 g of the compound prepared in Example 1, step D, are dissolved in 40 ml of anhydrous toluene and
05 treated with 3 g of Lawesson's reagent at 80°C under nitrogen. After 6 hours, the reaction is filtered and concentrated. The concentrate is chromatographed on silica using a DCM/ethyl acetate mixture (95/5; v/v) as the eluent to give the expected product
10 in the form of an oil, which crystallizes in the cold. m = 4.5 g. M.p. = 77-79°C.

- NMR spectrum:

0.90 ppm : t : 3 H : CH₃ (nBu)
1.20 ppm : s : 9 H : tBu
15 1.35 ppm : sext : 2 H : CH₃-CH₂-
1.60 ppm : quint : 2 H : CH₃-CH₂-CH₂-
1.80-2.10 ppm : m : 8 H : cyclopentane
2.60 ppm : t : 2 H : CH₃-CH₂-CH₂-CH₂-
5.35 ppm : s : 2 H : CH₂-C₆H₄-
20 7.25-7.80 ppm : m : 8 H : aromatic protons

B) 2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-thione trifluoroacetate

225 mg of the compound obtained in step A are
25 treated with 5 ml of DCM and 5 ml of TFA for 30 minutes. After concentration, the residue is taken up in ether. The expected compound is obtained in the form of a yellow powder, which is filtered off and then rinsed with hexane. m = 160 mg. M.p. = 185-190°C.

30 - Mass spectrum:

MH⁺ : 421

- NMR spectrum:

0.78 ppm : t : 3 H : CH₃ (nBu)
1.20 ppm : sext : 2 H : CH₃-CH₂-
35 1.50 ppm : quint : 2 H : CH₃-CH₂-CH₂-



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1.75-2.00 ppm : m : 8 H : cyclopentane
2.40 ppm : t : 2 H : $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2$
5.20 ppm : s : 2 H : $\text{CH}_2\text{-C}_6\text{H}_4\text{-}$
7.00-7.65 ppm : m : 8 H : aromatic protons

05

EXAMPLE 12

2-n-Butyl-4-(2-spiroindane)-1-[(2'-tert-butoxy-carbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one and 2-n-butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-(2-spiroindane)-2-imidazolin-5-one - Method 1

10

A) 2-Aminoindane-2-carboxylic acid is prepared according to R.M. Pinder, J. Med. Chem., 1971, 14, 9, 892, and the corresponding ethyl ester is then prepared according to Adkins (ref. cited in Example 2A).

15

B) 2-n-Butyl-4-(2-spiroindane)-2-imidazolin-5-one

2.78 g of the ethyl ester prepared in step A and 2.5 g of ethyl valerimide are dissolved in 20 ml of xylene in the presence of 60 μl of acetic acid and refluxed for 3 hours. A further 500 mg of ethyl valerimide are added and reflux is maintained for a further 3 hours. The reaction medium is concentrated and then chromatographed on silica using a hexane/ethyl acetate/acetic acid mixture (3/8/0.3; v/v/v) as the eluent. The pure fractions are combined and evaporated with toluene to give 3.07 g of the expected product in the form of a white solid. M.p. = 148-150°C.

20

25

- NMR spectrum:

0.90 ppm : t : 3 H : CH_3 (nBu)

30

1.2-1.7 ppm : m : 4 H : $\text{CH}_2\text{-CH}_2\text{-CH}_3$

2.4 ppm : t : 2 H : $\text{CH}_2\text{-(CH}_2\text{)}_2\text{-CH}_3$

2.8-3.2 ppm : q : 4 H : 2CH_2 (indane)

4.90 ppm : s : 2 H : $\text{CH}_2\text{-C}_6\text{H}_4\text{-}$

7.2 ppm : m : 4 H : aromatic protons

35

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C) 2-n-Butyl-4-(2-spiroindane)-1-[(2'-tert-butoxy-carbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one

The compound obtained in the previous step is dissolved in 20 ml of anhydrous DMF and treated with
05 450 mg of sodium methylate under nitrogen. After 20 minutes at room temperature, 3.6 g of 4-bromomethyl-2'-tert-butoxycarbonylbiphenyl are added and the mixture is stirred at 40°C for 6 hours. The reaction medium is concentrated, the usual washes are then carried out and
10 the product is chromatographed on silica using dichloromethane/ethyl acetate (95/5; v/v) as the eluent the expected compound in the form of a foam (m = 1.84 g).

- NMR spectrum:

15 0.80 ppm : t : 3 H : CH₃ (nBu)
1.20 ppm : s : 9 H : tBu
1.20-1.60 ppm : m : 4 H : CH₂-CH₂-CH₃
2.40 ppm : t : 2 H : CH₂-(CH₂)₂-CH₃
2.9-3.3 ppm : q : 4 H : 2CH₂ (indane)
20 4.80 ppm : s : 2 H : N-CH₂-C₆H₄-
7.20-7.80 ppm : m : 12 H : aromatic protons

D) 2-n-Butyl-1-[(2'-carboxybiphenyl-4-yl)methyl]-4-(2-spiroindane)-2-imidazolin-5-one

1.71 of the compound obtained in the
25 previous step are dissolved in 15 ml of DCM and treated with 20 ml of TFA. After 30 minutes, the reaction medium is concentrated and then taken up in ether. After trituration, the solid obtained is filtered off, rinsed with ether and dried to give 1.42 g of the
30 expected product. M.p. = 217-218°C.

- NMR spectrum:

0.70 ppm : t : 3 H : CH₃ (nBu)
1.10-1.50 ppm : m : 4 H : CH₂-CH₂-CH₃
2.30 ppm : t : 2 H : CH₂-(CH₂)₂-CH₃
35 2.8-3.3 ppm : q : 4 H : 2CH₂ (indane)

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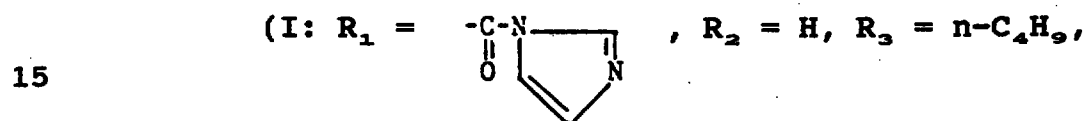
4.70 ppm : s : 2 H : $\text{N-CH}_2\text{-C}_6\text{H}_4\text{-}$

7.1-7.7 ppm : m : 12 H : aromatic protons

Other compounds according to the invention were prepared by one of the methods described above. They are collated in Table 1. The structure of each of these compounds is consistent with the analysis of their NMR spectra.

EXAMPLE 13

2-n-Butyl-1-[(2'-(imidazol-1-ylcarbonyl)bi-phenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-one



$\text{CR}_4\text{R}_5 = \text{cyclopentane}$, $\text{X} = \text{O}$)

A mixture containing 404 mg of the compound prepared in Example 1, step E, 15 ml of THF and 260 mg of carbonyldiimidazole is stirred at room temperature for 72 hours. The reaction medium is evaporated, the residue is taken up in ethyl acetate and the mixture is washed with water and then with a solution of sodium chloride to give 420 mg of product, which are purified by chromatography on silica using a DCM/ethyl acetate mixture (70/30; v/v) as the eluent to give the expected compound.

m = 230 mg.
M.p. = 120°C.

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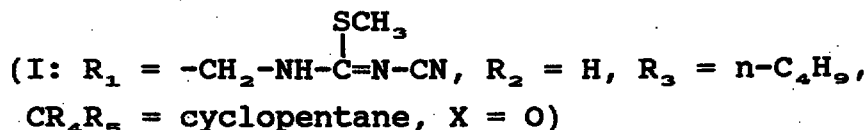


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EXAMPLE 14

2-n-Butyl-1-[(2'-(3-cyano-2-methylisothio-
ureidomethyl)biphenyl-4-yl)methyl]-4-spirocyclopentane-
2-imidazolin-5-one

05



- 10 A) 1-[(2'-Aminomethylbiphenyl-4-yl)methyl]-2-n-butyl-4-
spirocyclopentane-2-imidazolin-5-one

This compound is obtained by hydrogenation of
the compound prepared in Example 5.

- 15 1 g of the compound prepared in Example 5, step
A, is placed in 15 ml of absolute methanol and 2.3 ml
of ethanol in the presence of 0.5 g of 5% palladium-on-
charcoal and the mixture is hydrogenated at room tem-
perature for 24 hours. After treatment, 730 mg of the
expected product are obtained in the form of an oil.

- 20 B)

- A mixture containing 300 mg of the compound
prepared in the previous step and 113 mg of N-cyan-
imido-S,S-dimethyldithiocarbonate in 3 ml of ethanol is
refluxed for 24 hours. After the usual treatment, the
25 reaction medium is purified by chromatography on silica
using a DCM/ethyl acetate mixture (50/50; v/v) as the
eluent. The expected product is isolated in the form
of a white solid.

m = 307 mg.

- 30 M.p. = 83°C.

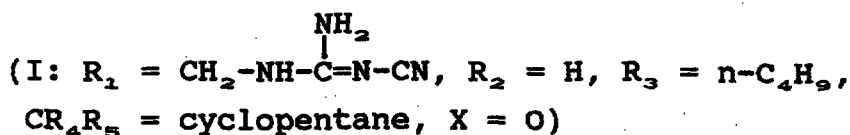
EXAMPLE 15

2-n-Butyl-1-[(2'-(2-cyanoguanidinomethyl)bi-
phenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-
35 one

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05 This compound is obtained from the compound
prepared in the previous Example. 200 mg of the com-
pound are placed in 10 ml of absolute ethanol and the
mixture is saturated with ammonia at about 10°C and
then heated at 80°C in an autoclave overnight. After
10 concentration of the reaction medium to dryness, the
residue is chromatographed on silica using a DCM/
methanol mixture (95/5; v/v) as the eluent to give 130
mg of the expected product.

M.p. = 100°C.

15

EXAMPLE 16

2-n-Butyl-4-spirocyclopentane-1-[(2'-trifluoro-
methysulfonylaminobiphenyl-4-yl)methyl]-2-imidazolin-
5-one trifluoromethylsulfonate

20

**A) 4-Methyl-2'-nitrobiphenyl**

25

11.2 g of 2-nitrobromobenzene are mixed with
15 g of 4-iodotoluene and the mixture is heated to
195°C and stirred at this temperature for 3 and a half
hours. After returning to room temperature, it is
taken up in DCM and heated to the reflux point, the hot
30 solution is filtered on Celite® and the DCM is then
evaporated off.

m = 6.5 g.

B.p. = 80-120°C under 0.2 mm Hg, $n_D^{24} = 1.6042$.

B) 4-Bromomethyl-2'-nitrobiphenyl

35

A mixture containing 6.5 g of 4-methyl-2'-





nitrobiphenyl, 5.42 g of NBS, 118 mg of azo-bis-iso-butyronitrile and 500 ml of carbon tetrachloride is refluxed for 5 hours. It is cooled to 0°C and filtered and the filtrate is concentrated to give 9 g of an oily product, which is used as such in the next step.

05

C) 2-n-Butyl-1-[(2'-nitrobiphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-one

A mixture containing 260 mg of 80% sodium hydride in 5 ml of DMF is prepared and 500 mg of 2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one, prepared in Example 2, step A, are added at room temperature under nitrogen. After stirring for 15 minutes, 901 mg of 4-bromomethyl-2'-nitrobiphenyl in 5 ml of DMF are added and stirring is continued for 24 hours. The reaction medium is concentrated to dryness and the residue is taken up in a water/ethyl acetate mixture. The organic phase is decanted, dried over sodium sulfate and filtered and the ethyl acetate is then evaporated off. The product obtained is chromatographed on silica using a DCM/ethyl acetate mixture (9/1; v/v) as the eluent to give 500 mg of the expected product.

10

15

20

D) 1-[(2'-Aminobiphenyl-4-yl)methyl]-2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one

450 mg of the product obtained in the previous step are placed in 10 ml of methanol in the presence of 5% palladium-on-charcoal, at room temperature, for hydrogenation. After filtration of the catalyst and evaporation, 240 mg of the expected product are obtained.

25

30

E)

In 4 ml of DCM, 225 mg of the product obtained in the previous step are mixed with 0.1 ml of triethylamine, 0.2 ml of trifluoromethylsulfonic anhydride is added under argon at -78°C and the mixture is then left to return to room temperature. The reaction

35

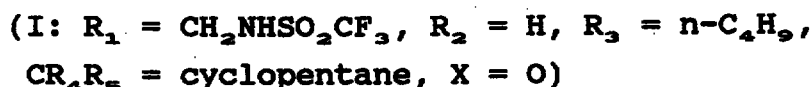
medium is washed with water and a solution of sodium bicarbonate and then dried and concentrated to give 150 mg of an amorphous white solid.

- NMR spectrum:

05 0.4-1.3 ppm : m : 7 H : $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-}$
1.4-2.3 ppm : m : 10 H : $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-CH}_2\text{-}$ and cyclo-
pentane
4-4.8 ppm : AB system : 2 H : $\text{N-CH}_2\text{-C}_6\text{H}_4\text{-}$
7-7.6 ppm : m : 8 H : aromatic protons
10 8.3 ppm : s : 1 H : -NH
10 ppm : sb : 1 H : $\text{CF}_3\text{SO}_3\text{H}$

EXAMPLE 17

2-n-Butyl-4-spirocyclopentane-1-[(2'-trifluoro-
15 methylsulfonylaminomethylbiphenyl-4-yl)methyl]-2-imidazolin-5-one trifluoromethylsulfonate



20

The preparation is effected starting from the 1-[(2'-aminomethylbiphenyl-4-yl)methyl]-2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one prepared in Example 14, step A. 322 mg of this compound and 0.122 ml of triethylamine are placed in 3.4 ml of DCM at -70°C and 0.294 ml of trifluoromethylsulfonic anhydride is added. The mixture is left to return to room temperature, poured into dilute acetic acid and extracted with DCM, the extract is dried over sodium sulfate and filtered and the DCM is evaporated off. The residue is chromatographed twice on silica using DCM/ethyl acetate (95/5; v/v, then 99.5/0.5; v/v) as the eluent.

This gives $m = 90$ mg.

M.p. = 90°C.

35

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- NMR spectrum:

0.4-1.2 ppm : m : 7 H : $-\text{CH}_2-\text{CH}_2-\text{CH}_3$

1.3-2.45 ppm : m : 10 H : $\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{CH}_3$ and cyclo-
pentane

05 4.1-5 ppm : m : 4 H : $\text{N}-\text{CH}_2-\text{C}_6\text{H}_4-$ and $\text{NH}-\text{CH}_2-\text{C}_6\text{H}_4-$

7.1-7.7 ppm : m : 8 H : aromatic protons

8.4 ppm : s : 1 H : NH

EXAMPLE 18

10 2-n-Butyl-1-[(2'-(N-hydroxyacetamide)biphenyl-
4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-one

(I: $\text{R}_1 = -\text{CO}-\text{NHOH}$, $\text{R}_2 = \text{H}$, $\text{R}_3 = n\text{-C}_4\text{H}_9$,
 $\text{CR}_4\text{R}_5 = \text{cyclopentane}$, $\text{X} = \text{O}$)

15

The compound prepared in Example 2 is freed from its trifluoroacetic acid salt by taking up this compound in an ethyl acetate/water mixture and bringing the solution to pH 6 by the addition of a saturated
20 solution of sodium bicarbonate. The organic phase is washed with a saturated solution of sodium chloride, dried over sodium sulfate, filtered and concentrated to give the free base in the form of a white solid.

450 mg of this compound are dissolved in
25 chloroform, 860 ml of thionyl chloride are added at 0°C and the mixture is stirred at room temperature for 2 hours. The solution is concentrated and the traces of thionyl chloride are removed by azeotropic distillation with toluene. The acid chloride thus obtained is added
30 dropwise in DMF solution to a solution containing 200 mg of hydroxylamine hydrochloride and 700 µl of DIPEA in 10 ml of DMF. After 2 hours at 0°C, the reaction medium is concentrated and the concentrate is taken up in 100 ml of DCM and 50 ml of water. The mixture is
35 brought to pH 7 and the organic phase is extracted and

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then dried over sodium sulfate. After filtration, the solution is concentrated. The product obtained is recrystallized from an ethyl acetate/ethyl ether/hexane mixture.

05 m = 360 mg.
 M.p. = 85°C.

EXAMPLE 19

2-n-Butyl-4-spirocyclopentane-1-[(2'-ureido-
10 biphenyl-4-yl)methyl]-2-imidazolin-5-one

(I: $R_1 = \text{NHCONH}_2$, $R_2 = \text{H}$, $R_3 = n\text{-C}_4\text{H}_9$,
 $\text{CR}_4\text{R}_5 = \text{cyclopentane}$, $\text{X} = \text{O}$)

15 This compound is prepared using the method described by B.B. Kobu et al. in Org. Synth., 1957, 37, 52, starting from the 1-[(2'-aminobiphenyl-4-yl)-methyl]-2-n-butyl-4-spirocyclopentane-2-imidazolin-5-one prepared in Example 14, step A.

20 1 g of the latter is dissolved in 50 ml of 6 N hydrochloric acid and treated with potassium isocyanate for 1 hour at 5°C. The reaction medium is concentrated, the concentrate is taken up in ethyl acetate and the mixture is washed with sodium bicarbonate and then
25 with a saturated solution of sodium chloride. After drying over sodium sulfate and filtration, the solution is concentrated and the oil obtained is purified by chromatography on silica using a DCM/methanol mixture (9/1; v/v) as the eluent.

30 m = 600 mg.

- NMR spectrum:

0.85 ppm : t : 3 H : $\text{CH}_2\text{-CH}_3$

1.35 ppm : sext : 2 H : $\text{CH}_2\text{-CH}_3$

1.6 ppm : quint : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_3$

35 1.7-2 ppm : m : 8 H : cyclopentane

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2.45 ppm : t : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$ 4.8 ppm : s : 2 H : $\text{-CH}_2\text{-C}_6\text{H}_4\text{-}$ 6.05 ppm : s : 2 H : NH_2 7-8 ppm : m : 9 H : 8 aromatic H + NHCO

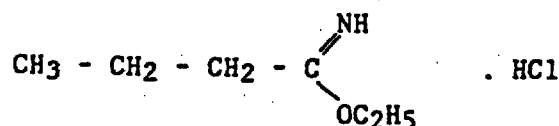
05

EXAMPLES 20 AND 21

1-[(2'-Carboxybiphenyl-4-yl)methyl]-2-n-propyl-
4-spirocyclohexane-2-imidazolin-5-one and 1-[(2'-N-
cyanocarboxamidebiphenyl-4-yl)methyl]-2-n-propyl-4-
10 spirocyclohexane-2-imidazolin-5-one

(I: $\text{R}_1 = \text{CO-NH-CN}$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{n-C}_3\text{H}_7$,
 $\text{CR}_4\text{R}_5 = \text{cyclohexane}$, $\text{X} = \text{O}$)

15 A) Ethyl butyrimidate hydrochloride



20

This compound is prepared according to Mc
Elvain (J. Amer. Chem. Soc., 1942, 64, 1825-1827).

23 ml of butyronitrile are added at 0°C to a
solution of 10.6 g of gaseous hydrochloric acid in 20
25 ml of anhydrous ethanol and then, after the reaction
medium has been left to stand for 4 days at 0°C , it is
poured into 200 ml of anhydrous ether at 0°C , with
stirring; the precipitate formed is filtered off,
washed with ether and then dried under vacuum to give
30 25.8 g of the expected product.

B) Ethyl butyrimidate

16 g of the imidate obtained in step A are
dissolved in 100 ml of dichloromethane and 50 ml of
water, and 15 g of potassium carbonate are added.
35 After decantation, the dichloromethane is dried over



potassium carbonate and then evaporated off to dryness without heating.

C) Ethyl ester of 1-aminocyclohexane acid

1-Aminocyclohexanecarboxylic acid is commercially available. 15 g of this amino acid are added at 0°C to a solution of 23 g of gaseous hydrochloric acid in 150 ml of anhydrous ethanol. The reaction medium is refluxed for 5 hours and then concentrated to dryness and the residue is taken up in ether. The white solid obtained is filtered off, washed with ether and then dissolved in a mixture of 300 ml of ether and 100 ml of water. The pH is brought to 9 by the addition of a solution of potassium carbonate. The organic phase is decanted, washed with a saturated solution of sodium chloride, dried over sodium sulfate and then evaporated to dryness to give 14 g of the expected product in the form of an oil.

D) 2-n-Propyl-4-spirocyclohexane-2-imidazolin-5-one

14 g of the product obtained in step C are dissolved in 200 ml of xylene containing 0.6 ml of acetic acid. Half the imidate obtained in step B is added and the mixture is heated to the reflux point. After 1 and a half hours, half the remaining imidate is added and the last quarter is then added after 4 hours. After a total reflux time of 7 hours, the medium is evaporated to dryness. The solid obtained is taken up in hexane, filtered off, washed with ether and then dried.

This gives 10.3 g of the expected imidazolinone.

M.p. = 124-125°C.

- IR (CHCl₃):

1715 cm⁻¹ : C=O

1635 cm⁻¹ : C=N

Note: The compound present in solution is indeed an



imidazolin-5-one according to the values of the IR bands.

E) 2-n-Propyl-4-spirocyclohexane-1-[(2'-tert-butoxy-carbonylbiphenyl-4-yl)methyl]-2-imidazolin-5-one

05 970 mg of the imidazolinone obtained in step D are added to 0.24 g of sodium hydride as an 80% dispersion in oil, suspended in 10 ml of dimethylformamide. After stirring for 20 minutes under nitrogen, 1.91 g of 4-bromomethyl-2'-tert-butoxycarbonylbiphenyl, prepared
10 according to European patent application 324 377, are added over 5 minutes. After stirring for 1 hour, the medium is concentrated to half its volume under vacuum and taken up in 100 ml of ethyl acetate and then in 20 ml of water. The organic phase is decanted, washed
15 with a saturated solution of sodium chloride, dried over sodium sulfate and then concentrated under vacuum. The residue is chromatographed on silica using an ethyl acetate/toluene mixture as the eluent to give 2.10 g of the expected product in the form of a wax.

20 - IR (CHCl_3):

1705-1715 cm^{-1} : C=O, C=O (ester, imidazolinone)

1635 cm^{-1} : C=N

Analysis of the NMR spectrum confirms the structure.

25 F) 1-[(2'-Carboxybiphenyl-4-yl)methyl]-2-n-propyl-4-spirocyclohexane-2-imidazolin-5-one (Example 20)

1.25 g of the tert-butyl ester obtained in step E are stirred for 45 minutes in a mixture of 11 ml of dichloromethane and 15 ml of trifluoroacetic acid. After concentration under vacuum, the residue is taken
30 up in ether. The solid formed is filtered off, washed with ether and then dried to give 1.04 g of a white solid.

M.p. = 170-172°C.

- NMR spectrum:

35 7.10-7.80 ppm : m : 8 H : aromatic protons

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4.90 ppm : s : 2 H : $\text{N-CH}_2\text{-C}_6\text{H}_4\text{-}$ 2.45 ppm : t : 2 H : $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-}$ 1.40-1.80 ppm : m : 12 H : spirocyclohexane + $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-}$ 05 0.90 ppm : t : 3 H : $\text{CH}_3\text{-CH}_2\text{-CH}_2\text{-}$

1.60 g of the trifluoroacetate obtained previously are dissolved in 150 ml of ethyl acetate and 20 ml of water. 1 N sodium hydroxide solution is added to bring the pH to 5.0. The organic phase is decanted,
10 washed with a saturated solution of sodium chloride, dried over sodium sulfate and then evaporated to dryness. The solid residue is taken up in ethyl ether, filtered off and dried.

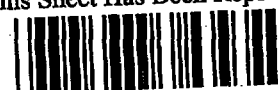
m = 1.14 g.

15 M.p. = 208-210°C.

G) 1-[(2'-N-Cyanocarboxamidebiphenyl-4-yl)methyl]-2-propyl-4-spirocyclopentane-2-imidazolin-5-one
(Example 21)

0.54 ml of thionyl chloride is added to 300 mg
20 of the compound prepared in the previous step, suspended in 5 ml of DCM. After 1 and a half hours, the reaction medium is concentrated under vacuum and then evaporated twice with benzene. The acid chloride thus obtained is dissolved in 2 ml of dioxane and added to a
25 solution of 42 mg of cyanamide in 1 ml of dioxane containing 0.2 ml of 10 N sodium hydroxide solution. After 1 and a half hours, the reaction medium is diluted with 150 ml of ethyl acetate and 20 ml of water, the pH is brought to 5 with acetic acid and the organic
30 phase is decanted, washed with a saturated solution of sodium chloride, dried over sodium sulfate and then evaporated to dryness. The residue is chromatographed on silica using a chloroform/methanol/acetic acid mixture (90/8/2; v/v) as the eluent to give 160 mg of the
35 expected product in the form of a solid.

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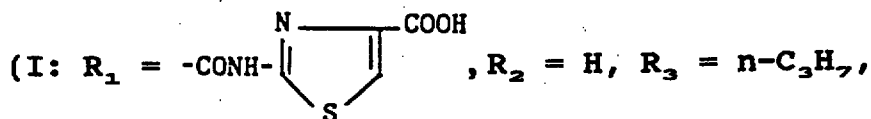


- 64 -

- IR (KBr):
2150 cm^{-1} : $\text{C}\equiv\text{N}$
- Mass spectrum:
 MH^+ : 429
- 05 - NMR spectrum:
7.20-7.70 ppm : m : 8 H : aromatic protons
4.75 ppm : s : 2 H : $\text{N}-\text{CH}_2-\text{C}_6\text{H}_4-$
2.40 ppm : t : 2 H : $\text{CH}_3-\text{CH}_2-\text{CH}_2-$
1.30-1.80 ppm : m : 12 H : $\text{CH}_3-\text{CH}_2-\text{CH}_2-$ and spiro-
10 cyclohexane
0.85 ppm : t : 3 H : $\text{CH}_3-\text{CH}_2-\text{CH}_2$

EXAMPLE 22

- 1-[(2'-(N-4-carboxy-1,3-thiazol-2-ylacetamide)-
15 biphenyl-4-yl)methyl]-2-n-propyl-4-spirocyclohexane-2-
imidazolin-5-one



$\text{CR}_4\text{R}_5 = \text{cyclohexane}$, $\text{X} = \text{O}$)

- 25 This compound is prepared from the compound
obtained in Example 20.

2-Amino-4-ethoxycarbonyl-1,3-thiazole is prepared according to B. Plouvier et al., J. Heterocycl. Chem., 1989, 26(6), 1646.

- 30 A) 1-[(N-4-Carbethoxy-1,3-thiazol-2-ylacetamide)-
methyl]-2-n-propyl-4-spirocyclohexane-2-imidazolin-5-
one

- 35 500 mg of BOP and 0.14 ml of triethylamine are added to a solution of 404 mg of the compound prepared in Example 20 and 190 mg of thiazole derivative in 4 ml of DCM and 1 ml of DMF. The mixture is stirred for 40

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hours at room temperature and then 7 hours at 50°C. The reaction medium is taken up in 50 ml of ethyl acetate and washed twice with a KHSO_4 - K_2SO_4 solution, then twice with a saturated solution of sodium bicarbonate and then once with a saturated solution of sodium chloride. After drying over sodium sulfate, the organic phase is concentrated under vacuum and the residue is chromatographed on silica using an ethyl acetate/toluene mixture as the eluent to give 120 mg of the expected product.

M.p. = 96-98°C.

B)

0.5 ml of 2 N sodium hydroxide solution is added to 110 mg of the product obtained in the previous step, dissolved in 1 ml of methanol and 1 ml of dioxane. After stirring for 35 minutes, the reaction medium is diluted with 10 ml of water and 60 ml of ethyl acetate and the pH is brought to 5 by the addition of 1 N hydrochloric acid. The organic phase is decanted, washed with a saturated solution of sodium chloride, dried over sodium sulfate and then concentrated. The residue is taken up in ether, filtered off and dried.

m = 100 mg.

M.p. = 145-148°C.

- NMR spectrum:

8.0 ppm : s : 1 H : H in the 5 position of the thiazole

7.1-7.7 ppm : m : 8 H : aromatic protons

4.7 ppm : s : 2 H : $\text{N-CH}_2\text{-C}_6\text{H}_4\text{-}$

2.25 ppm : t : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_3$

1.2-1.8 ppm : m : 12 H : cyclohexane and $\text{CH}_2\text{-CH}_2\text{-CH}_3$

0.85 ppm : t : 3 H : $\text{CH}_2\text{-CH}_2\text{-CH}_3$

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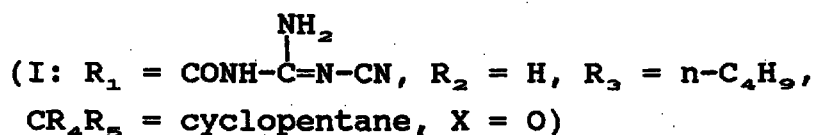


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EXAMPLE 23

2-n-Butyl-1-[(2'-(2-cyanoguanidinocarbonyl)-
biphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-
5-one

05

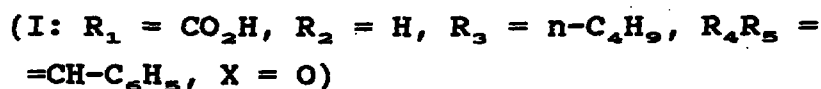


10 The acid chloride of the compound obtained in
Example 2 is prepared. 1 g of this compound is placed
in 20 ml of DCM, in the presence of 1.8 ml of thionyl
chloride, and the mixture is stirred at room tempera-
15 ture for 2 hours. After concentration of the medium,
the residue is taken up in benzene and the mixture is
then concentrated again. The crude product isolated is
then used. It is mixed with 417 mg of dicyanodiamide,
0.5 ml of 10 N sodium hydroxide solution, 0.5 ml of
20 water and 10 ml of dioxane and the mixture is then
stirred for 5 hours. The reaction medium is taken up
in water and ethyl acetate, potassium carbonate is
added and the mixture is then concentrated. The resi-
25 due obtained is chromatographed on silica using a DCM/
methanol mixture (95/5; v/v) as the eluent. 100 mg of
the expected product are isolated.

M.p. = 105°C.

EXAMPLE 24

30 4-Benzylidene-2-n-butyl-1-[(2'-carboxybiphenyl-
4-yl)methyl]-2-imidazolin-5-one trifluoroacetate



35

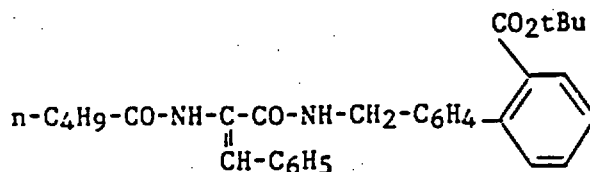
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A) Tert-butyl 4-(1-benzylidene-1-valerylaminomethyl-
amidomethyl)biphenyl-2-carboxylate

05



Starting from N-Boc- α -dehydro-(L)-phenylal-
nine, the N-carboxyanhydride of α -dehydro-(L)-phenyl-
alanine is prepared according to R. Jacquier et al.,
Tetrahedron Lett., 1984, 25(26), 2775. p. 644
mg of tert-butyl 4-aminomethylbiphenyl-2'-carboxylate
are added to a solution of 430 mg of this compound in 5
ml of THF, the mixture is stirred for 2 hours at room
temperature, 1 ml of methyl orthovalerate is then added
and the mixture is evaporated to dryness under vacuum
without heating. The residue is heated for 3 hours at
100°C, concentrated under vacuum and then chromato-
graphed on silica using a hexane/ethyl acetate mixture
(4/1; v/v) as the eluent to give 580 mg of a white
solid.

M.p. = 154°C.

- NMR spectrum:

1.3 ppm : s : 9 H : tBu
0.65 ppm : t : 3 H : CH₃ (nBu)
2 ppm : t : 2 H : CH₃-CH₂-CH₂-CH₂-CO
4.4 ppm : d : 1 H : CH₂-NH
6.8 ppm : s : 1 H : CH (=CH-C₆H₅)

B) 4-Benzylidene-2-n-butyl-1-[(2'-tert-butoxycarbonyl-
biphenyl-4-yl)methyl]-2-imidazolin-5-one

440 mg of the compound obtained in step A are
dissolved in 1 ml of acetic acid and heated for 30
minutes at 100°C.

The solution is evaporated to dryness under



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vacuum and the residue is chromatographed on silica using a hexane/ethyl acetate mixture (4/1; v/v) as the eluent to give 130 mg of the expected product in the form of an oil.

05 - NMR spectrum:

4.9 ppm : s : 2 H : CH_2 ($\text{N}-\text{CH}_2-\text{C}_6\text{H}_4-$)

C)

10 100 mg of the compound obtained in the previous step are dissolved in 1 ml of DCM, 1 ml of trifluoroacetic acid is added and the mixture is then stirred for 40 minutes at room temperature and evaporated under vacuum. The residue is taken up several times in DCM and then evaporated. A white solid precipitates on the addition of ethyl ether.

15 m = 101 mg.

M.p. = 85°C.

- Mass spectrum:

MH^+ : 439

- NMR spectrum:

20 0.82 ppm : t : 3 H : CH_3 (nBu)

1.3 ppm : sext : 2 H : CH_3-CH_2-

1.6 ppm : m : 2 H : $\text{CH}_3-\text{CH}_2-\text{CH}_2-$

2.6 ppm : t : 2 H : $\text{CH}_3-\text{CH}_2-\text{CH}_2-\text{CH}_2-$

4.82 ppm : s : 2 H : $\text{CH}_2-\text{C}_6\text{H}_4-$

25 7.05 ppm : s : 1 H : $=\text{CH}-\text{C}_6\text{H}_5$

7.2-8.2 ppm : m : 13 H : aromatic protons

EXAMPLE 25

30 4-Benzylidene-1-[(2'-carboxybiphenyl-4-yl)-methyl]-2-phenyl-2-imidazolin-5-one

(I: $\text{R}_1 = \text{CO}_2\text{H}$, $\text{R}_2 = \text{H}$, $\text{R}_3 = \text{C}_6\text{H}_5$, $\text{R}_4\text{R}_5 =$
 $=\text{CH}-\text{C}_6\text{H}_5$, $\text{X} = \text{O}$)

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A) 4-Benzylidene-2-phenyloxazol-5-one

1.8 g of hippuric acid and 0.4 g of potassium bicarbonate are dissolved in 4 ml of acetic anhydride, the solution is heated for a few minutes at 50°C and then cooled to room temperature and 1.49 g of benzaldehyde are added. After 1 hour at room temperature, 20 ml of distilled water are added at 80°C. The solid which precipitates is filtered off, washed with water and ethanol and then dried to give 1.24 g of the expected product in the form of a yellow solid.

M.p. = 215°C.

- NMR spectrum:

7.4 ppm : s : 1 H : =CH-C₆H₅

8.1-8.4 ppm : m : 10 H : aromatic protons

15 B) Tert-butyl 4-(1-benzoylamino-1-benzylidenemethyl-amidomethyl)biphenyl-2'-carboxylate

A mixture containing 500 mg of the compound obtained in the previous step, 570 mg of tert-butyl 4-aminomethylbiphenyl-2'-carboxylate and 10 ml of pyridine is heated at 110°C for 3 hours. It is evaporated under vacuum, the residue is taken up in chloroform and the mixture is then evaporated again. The residue is chromatographed on silica using a hexane/ethyl acetate mixture (3/1 then 2/1; v/v) as the eluent to give 106 mg of the expected product in the form of a yellow solid.

- NMR spectrum:

1.1 ppm : s : 9 H : tBu

4.35 ppm : t : 2 H : -CH₂-NH

30 7.05-7.06 ppm : m : 19 H : aromatic protons +

C₆H₅-CH=8.65 ppm : t : 1 H : NH-CH₂

9.9 ppm : s : 1 H : NH-CH=

C)

35 A mixture of 1.2 g of the compound obtained in

- 70 -

the previous step and 1.1 g of freshly melted sodium acetate is refluxed for 6 hours in 5 ml of acetic acid. It is left to cool and an insoluble material is then precipitated by the addition of chloroform. The filtrate is evaporated and the residue is chromatographed on silica using a chloroform/methanol mixture (98/2; v/v) as the eluent. The solid obtained is recrystallized from ethyl ether.

m = 692 mg.

M.p. = 120°C.

- NMR spectrum:

4.95 ppm : s : 2 H : $\text{CH}_2\text{-C}_6\text{H}_4\text{-}$

7.1-8.3 ppm : m : 19 H : aromatic protons + $\text{=CH-C}_6\text{H}_5$

EXAMPLES 26 AND 27

2-n-Butyl-1-[(2'-(2-methyltetrazol-5-yl)biphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-one (Example 26) and 2-n-butyl-1-[(2'-(1-methyltetrazol-5-yl)biphenyl-4-yl)methyl]-4-spirocyclopentane-2-imidazolin-5-one (Example 27)

In 10 ml of DMF, 500 mg of the compound prepared in Example 5 are mixed with 58 mg of sodium hydride, the mixture is stirred for 30 minutes, 179 mg of methyl iodide and 2 ml of DMF are then added and the mixture is stirred at room temperature for 4 hours. The reaction medium is concentrated and the concentrate is taken up in water and then extracted with ethyl acetate. The extract is dried over sodium sulfate and filtered and the solvent is evaporated off. The residue is chromatographed on silica using a hexane/ethyl acetate mixture (6/4; v/v) as the eluent. 2 fractions are isolated:

90 mg of the compound of Example 26
and 184 mg of the compound of Example 27



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- NMR spectra:

Example 26

- 0.7 ppm : t : 3 H : CH_3 - (nBu)
1.2 ppm : sext : 2 H : CH_3 - CH_2 -
05 1.4 ppm : quint: 2 H : CH_3 - CH_2 - CH_2 -
1.5-1.9 ppm : m : 8 H : cyclopentane
2.25 ppm : t : 2 H : CH_3 - CH_2 - CH_2 - CH_2 -
4.15 ppm : s : 3 H : N- CH_3
4.6 ppm : s : 2 H : -N- CH_2 - C_6H_4 -
10 7 ppm : AA', BB' system : 4 H : CH_2 - C_6H_4 -
7.3-7.75 ppm : m : 4 H : CH_2 - C_6H_4 - C_6H_4 -

Example 27

- 0.7 ppm : t : 3 H : CH_3 (nBu)
1.15 ppm : sext : 2 H : CH_3 - CH_2 -
15 1.38 ppm : quint : 2 H : CH_3 - CH_2 - CH_2 -
1.5-1.9 ppm : m : 8 H : cyclopentane
2.2 ppm : t : 2 H : CH_3 - CH_2 - CH_2 - CH_2 -
3.35 ppm : s : 3 H : N- CH_3
4.6 ppm : s : 2 H : N- CH_2 - C_6H_4
20 7 ppm : AA', BB' system : 4 H : N- CH_2 - C_6H_4 -
7.4-7.8 ppm : m : 4 H : CH_2 - C_6H_4 - C_6H_4 -

EXAMPLE 28

- 2-n-Butyl-6-spirocyclopentane-3-[(2'-(tetrazol-
25 5-yl)biphenyl-4-yl)methyl]-4(1H)-5,6-dihydropyrimidin-
4-one

A) Ethyl cyclopentylideneacetate

- 6 g of 80% sodium hydride are placed in 40 ml
of benzene, and 57.1 ml of ethyl triethylphosphono-
30 acetate are added dropwise at a temperature below 35°C.
After 1 hour at room temperature, 24.3 ml of cyclo-
pentanone are added dropwise. The mixture is heated at
65°C for 15 minutes and then cooled to room temperature
and the supernatant liquor is decanted. 25 ml of
35 benzene are added, the mixture is heated at 65°C for 15

- 72 -

minutes, cooled and decanted and the supernatant liquor is then recovered. The operation is repeated once. Evaporation of the liquors gives 42 g of the expected product, which is distilled.

05 B.p. = 102°C under 11 mm of mercury.
 m = 22.8 g.

B) (1-Aminocyclopentyl)acetamide

150 ml of gaseous ammonia are added to 20 g of the ethyl cyclopentylideneacetate prepared previously and the mixture is heated at 150°C for 72 hours. The product obtained after evaporation is purified by chromatography on silica using a DCM/methanol/20% aqueous ammonia mixture (90/10/1; v/v/v) as the eluent. The product obtained is dissolved in DCM and the solution is dried over sodium sulfate. It is filtered and the DCM is evaporated off to give 7.2 g of the expected product.

C) 2-n-Butyl-6-spirocyclopentane-4(1H)-5,6-dihydropyrimidin-4-one

20 A mixture containing 4.57 g of the (1-amino-cyclopentyl)acetamide prepared previously, 25 ml of methyl orthovalerate and a few drops of acetic acid is heated at 100°C for 18 hours. After evaporation of the excess orthovalerate, the residue is taken up in an ethyl acetate/sodium bicarbonate mixture, then washed with an aqueous solution of sodium chloride, dried that (sic) sodium sulfate and then purified by chromatography on silica using a DCM/methanol mixture (98/2; v/v) as the eluent.

30 m = 5 g.

- NMR spectrum:

0.75 ppm : t : 3 H : CH₃ (nBu)

1.2 ppm : sext : 2 H : CH₃-CH₂-

1.3-1.8 ppm : m : 10 H : CH₃-CH₂-CH₂ and cyclopentane

35 2 ppm : t : 2 H : CH₃-CH₂-CH₂-CH₂-



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2.15 ppm : s : 2 H : $\text{CH}_2\text{-CO}$ 9.95 ppm : sb : 1 H : NH

This compound is the one obtained in Example 10, step C.

- 05 D) 2-n-Butyl-4-spirocyclopentane-1-[(2'-(triphenyl-methyltetrazol-5-yl)biphenyl-4-yl)methyl]pyrimidin-6-one

327 mg of 80% sodium hydride in 30 ml of DMF are mixed for 30 minutes under nitrogen with 1.5 g of
10 the pyrimidinone prepared previously, and 5.27 g of 4-bromomethyl-2'-(triphenylmethyltetrazol-5-yl)biphenyl are added. After stirring for 4 hours at room temperature, the solvents are evaporated off and the residue is taken up in ethyl acetate and water, dried over
15 sodium sulfate and concentrated. The product obtained is purified by chromatography on silica using an ethyl acetate/hexane mixture (3/7; v/v) as the eluent.

m = 3.2 g.

E)

- 20 3 g of the compound obtained in the previous step are placed in 15 ml of methanol, the mixture is cooled in a water/ice bath, 2.2 ml of 4 N HCl are added and the mixture is stirred for 5 hours at room temperature. After evaporation, the residue is taken up in
25 ethyl acetate and water, and sodium hydroxide solution is then added to give a basic pH (pH 11). The mixture is left to decant and the aqueous phase is washed with ethyl ether and toluene and then ether again. This aqueous phase is brought to pH 5 by the addition of
30 dilute hydrochloric acid and is then extracted with ethyl acetate and the extract is dried and concentrated. The product obtained is purified on silica using a DCM/methanol mixture (95/5; v/v) as the eluent to give 800 mg of the expected product.

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- NMR spectrum:

- 0.85 ppm : t : 3 H : CH_3 (nBu)
 1.30 ppm : sext : 2 H : $\text{CH}_2\text{-CH}_2$
 1.40-1.95 ppm : m : 10 H : cyclopentane and
 05 $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$
 2.30 ppm : t : 2 H : $\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3$
 2.55 ppm : s : 2 H : $\text{CH}_2\text{-CO}$
 4.95 ppm : s : 2 H : $\text{N-CH}_2\text{-C}_6\text{H}_4\text{-}$
 7.05 ppm : m : 4 H : $\text{CH}_2\text{-C}_6\text{H}_4\text{-}$
 10 7.55-7.82 ppm : m : 4 H : $\text{CH}_2\text{-C}_6\text{H}_4\text{-C}_6\text{H}_4\text{-}$

EXAMPLE 29

2-n-Butyl-3-[(2'-carboxybiphenyl-4-yl)methyl]-
 5-spirocyclopentane-5(1H)-5,6-dihydropyrimidin-4-one
 15 trifluoroacetate

A) Ethyl 1-cyanocyclopentanecarboxylate

This compound is prepared according to Helv.
 Chim. Acta, 1952, 35(7), 2561.

9.2 g of sodium are dissolved in 200 cm³ of
 20 absolute ethanol. Half the solution of sodium ethylate
 formed is poured into a funnel. 24.88 g of ethyl
 cyanoacetate are added to the remaining half and the
 mixture is brought to the reflux point.

43.19 g of 1,4-dibromobutane are poured into
 25 another funnel and the solution of sodium ethylate and
 the 1,4-dibromobutane are simultaneously added dropwise
 to the reaction medium. When the addition is complete,
 reflux is maintained for 2 hours. The mixture is eva-
 30 porated and the residue is taken up in an ethyl ether/
 water mixture, washed with a saturated solution of
 sodium chloride and then dried. The product obtained
 distills at 115-120°C under 11 mm of mercury.

m = 24 g.

B) Ethyl 1-aminomethylcyclopentanecarboxylate

35 This compound is prepared by the catalytic



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hydrogenation of ethyl 1-cyanocyclopentanecarboxylate.

20 g of ethyl 1-cyanocyclopentanecarboxylate are placed in 200 ml of a 10% solution of ammonia in ethanol and hydrogenated at 60°C under a pressure of 100 bar in the presence of rhodium-on-alumina for 72 hours. After filtration on cellite® and evaporation, the residue is chromatographed on silica using a DCM/methanol/20% aqueous ammonia mixture (98/2/0.5; v/v/v) as the eluent.

10 m = 12.8 g.

C) 2-n-Butyl-5-spirocyclopentane-4(1H)-5,6-dihydropyrimidin-4-one

A mixture containing 13.12 g of the compound obtained in the previous step and 13.5 g of ethyl valerimide in 100 ml of xylene containing a few drops of acetic acid is refluxed for 13 hours. The reaction medium is evaporated and the residue is taken up in ethyl acetate and a 10% solution of sodium carbonate and then dried and concentrated.

20 m = 14 g.

M.p. = 89-91°C.

- NMR spectrum:

0.80 ppm : t : 3 H : CH₃ (nBu)

1.10-1.80 ppm : m : 12 H : CH₃-CH₂-CH₂- and cyclopentane

2.05 ppm : t : 2 H : CH₃-CH₂-CH₂-CH₂-

3.20 ppm : s : 2 H : CH₂ (pyrimidinone)

10 ppm : 1 H : s : NH-CO

D) 2-n-Butyl-5-spirocyclopentane-3-[(2'-tert-butoxycarbonylbiphenyl-4-yl)methyl]-4(1H)-5,6-dihydropyrimidin-4-one

500 mg of the product obtained in the previous step are placed in 40 ml of DMF in the presence of 115 mg of an 80% dispersion of sodium hydride in oil, under argon, and stirred at room temperature for half an

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hour. 1.08 g of 4-bromomethyl-2'-*tert*-butoxycarbonyl-biphenyl are added and the mixture is stirred for 2 hours. After evaporation, the residue is taken up in an ethyl acetate/water mixture, washed with a saturated solution of sodium chloride and then dried, concentrated and chromatographed on silica using an ethyl acetate/hexane mixture (3/7; v/v) as the eluent.

m = 280 mg.

E)

250 ml of the *tert*-butyl ester prepared in the previous step are dissolved in 10 ml of DCM. The solution is cooled in a bath of iced water, 5 ml of cold trifluoroacetic acid are then added and the mixture is stirred for one hour in the cold and then 1 hour at room temperature. It is evaporated under reduced pressure. The residue is taken up in ethyl ether and then evaporated. The operation is repeated 3 times, the evaporation residue is then taken up in hexane and triturated and the hexane is then decanted. The product is taken up in ethyl ether and the precipitate is filtered off.

m = 190 mg.

M.p. = 153-155°C.

- NMR spectrum:

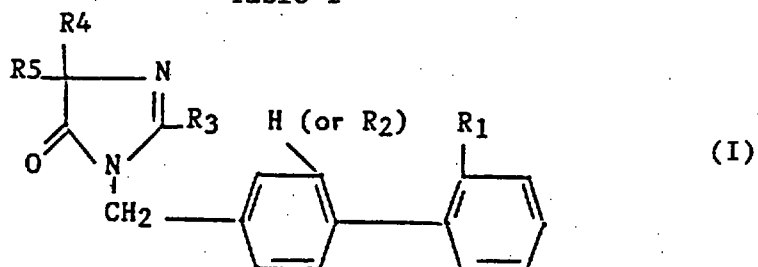
0.85 ppm : t : 3 H : CH₃ (nBu)
1.35 ppm : sext : 2 H : CH₃-CH₂-
1.45-2.20 ppm : m : 10 H : CH₃-CH₂-CH₂- and cyclopentane
2.80 ppm : t : 2 H : CH₃-CH₂-CH₂-CH₂-
3.80 ppm : s : 2 H : CH₂ (pyrimidinone)
5.15 ppm : s : 2 H : N-CH₂-
7.25 ppm : m : 8 H : aromatic protons

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Table 1



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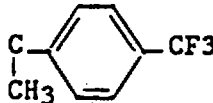
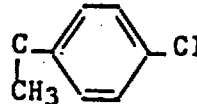
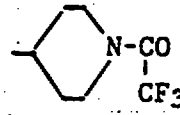
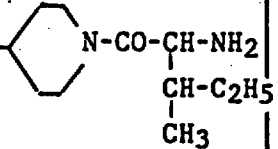
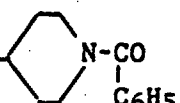
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(Ex.)	R ₁	R ₃	CR ₄ R ₅	Salt	M.p. °C
(30)	CO ₂ H	n-C ₄ H ₉	cyclohexane	TFA	172-174
(31)	CO ₂ CH ₃	n-C ₄ H ₉	cyclopentane	-	86-87
(32)*	CO ₂ H	n-C ₄ H ₉	C(CH ₃)C ₆ H ₅	TFA	55-60
(33)	CO ₂ H	n-C ₄ H ₉	C(C ₂ H ₅) ₂	TFA	82-84
(34)	CO ₂ H	n-C ₃ H ₇	cyclopentane	TFA	164
(35)	(**)	n-C ₄ H ₉	cyclopentane	-	163-164
(36)	CO ₂ H	C ₆ H ₅	cyclopentane	TFA	178
(37)	CO ₂ H	n-C ₄ H ₉	cycloheptane	TFA	160-162
(38)	CO ₂ H	CH ₃	cyclopentane	TFA	140
(39)	CO ₂ H	n-C ₄ H ₉	cyclopropane	-	204-205
(40)	tetrazol-5-yl	-CH ₂ -CH ₂ - CH=CH ₂	cyclopentane	-	110
(41)	tetrazol-5-yl	n-C ₄ H ₉	cyclohexane	-	130
(42)	tetrazol-5-yl	n-C ₃ H ₇	cyclohexane	-	141
(43)	CO ₂ H	cyclopentyl	cyclopentane	TFA	82-88
(44)	CO ₂ H	n-C ₅ H ₁₁	cyclopentane	TFA	151
(45)	CO ₂ H	CH ₂ -C ₆ H ₅	cyclopentane	TFA	88
(46)	CO ₂ H	H	cyclopentane	-	230
(47)	CO ₂ H	n-C ₄ H ₉	cyclobutane	TFA	178



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05	(48)	CO ₂ H	n-C ₄ H ₉	cyclododecane	TFA	130-135
	(49)	CO ₂ H	n-C ₄ H ₉	2-adamantane	TFA	164-166
	(50)	CO ₂ H	n-C ₄ H ₉	4-phenyl-cyclohexane	TFA	155-157
	(51)	CO ₂ H	n-C ₄ H ₉	4-methyl-cyclohexane	TFA	198-200
	(52)	CO ₂ H	n-C ₄ H ₉	N-acetyl-4-piperidine	TFA	90-95
10	(53)	CO ₂ H	C ₃ F ₇	cyclopentane	-	141-143
	(54)*	CO ₂ H	n-C ₄ H ₉		-	207-209
15	(55)*	CO ₂ H	n-C ₄ H ₉		TFA	105
	(56)	CO ₂ H	n-C ₄ H ₉		TFA	95-105
20	(57)	CO ₂ H	n-C ₄ H ₉		TFA	125-135
	(58)	CO ₂ H	n-C ₄ H ₉		TFA	85-90

25 ** R₁ = H and R₂ = CO₂H

* These compounds have an asymmetric carbon and are isolated in the form of a mixture of optical isomers.

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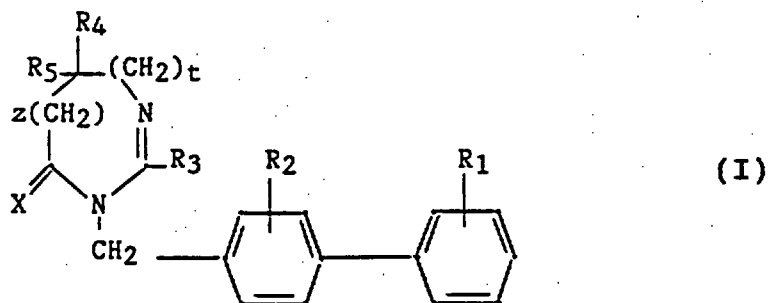


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WHAT IS CLAIMED IS:

1. A compound of the formula



in which:

- R_1 and R_2 are similar or different and are each independently hydrogen or a group selected from a C_1-C_6 alkyl, a C_1-C_4 alkoxy, an amino, an aminomethyl, a carboxyl, an alkoxycarbonyl in which the alkoxy is C_1-C_4 , a cyano, a tetrazolyl, a methyltetrazolyl, a methylsulfonylamino, a trifluoromethylsulfonylamino, a trifluoromethylsulfonylaminomethyl, an N-cyanoacetamide, an N-hydroxyacetamide, an N-(4-carboxy-1,3-thiazol-2-yl)acetamide, a ureido, a 2-cyano-guanidinocarbonyl, a 2-cyanoguanidinomethyl, an imidazol-1-ylcarbonyl and a 3-cyano-2-methylisothio-ureidomethyl, with the proviso that at least one of the substituents R_1 or R_2 is other than hydrogen;
- R_3 is a hydrogen, a C_1-C_6 alkyl which is unsubstituted or substituted by one or more halogen atoms, a C_2-C_6 alkenyl, a C_3-C_7 cycloalkyl, a phenyl, a phenylalkyl in which the alkyl is C_1-C_3 , or a phenylalkenyl in which the alkenyl is C_2-C_3 , said phenyl groups being unsubstituted or monosubstituted or polysubstituted by a halogen atom, a C_1-C_4 alkyl, a C_1-C_4 halogenoalkyl, a C_1-C_4 polyhalogenoalkyl, a hydroxyl or a C_1-C_4 alkoxy;





- R_4 and R_5 are each independently a C_1-C_6 alkyl, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3 , said alkyl, phenyl and phenylalkyl groups being unsubstituted or substituted by one or more halogen atoms or by a group selected from a C_1-C_4 perfluoroalkyl, a hydroxyl and a C_1-C_4 alkoxy;
 - or R_4 and R_5 together form a group of the formula $=CR_7R_8$, in which R_7 is hydrogen, a C_1-C_4 alkyl or a phenyl and R_8 is a C_1-C_4 alkyl or a phenyl;
 - or else R_4 and R_5 together are either a group of the formula $(CH_2)_n$ or a group of the formula $(CH_2)_pY-(CH_2)_q$, in which Y is either an oxygen atom, or a sulfur atom, or a carbon atom substituted by a C_1-C_4 alkyl group, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3 , or a group $N-R_6$, in which R_6 is a hydrogen, a C_1-C_4 alkyl, a phenylalkyl in which the alkyl is C_1-C_3 , a C_1-C_4 alkylcarbonyl, a C_1-C_4 halogenoalkylcarbonyl, a C_1-C_4 polyhalogenoalkylcarbonyl, a benzoyl, an alpha-aminoacyl or an N-protecting group, or R_4 and R_5 , together with the carbon atom to which they are bonded, form an indane or an adamantane;
 - $p + q = m$;
 - n is an integer between 2 and 11;
 - m is an integer between 2 and 5;
 - X is an oxygen atom or sulfur atom; and
 - z and t are zero or one is zero and the other is one; and its salts.
2. A compound according to claim 1 characterized in that R_1 is in the ortho position and is a carboxyl or tetrazolyl group and R_2 is hydrogen.
3. A compound according to claim 1 or claim 2 characterized in that R_4 and R_5 form a cyclopentane or a cyclohexane with the carbon to which they are bonded.
4. A compound according to any one of claims 1 to 3





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characterized in that R_3 is a linear C_1-C_6 alkyl group.

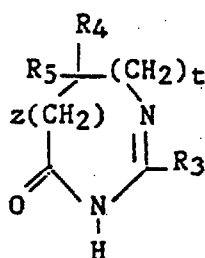
5. A compound according to any one of claims 1 to 4 characterized in that X is oxygen.

6. A compound according to any one of claims 1 to 5 characterized in that $z = t = 0$.

7. A compound according to claim 1 characterized in that it is the 2-n-butyl-4-spirocyclopentane-1-((2'-(tetrazol-5-yl)biphenyl-4-yl)methyl)-2-imidazolin-5-one or one of its salts with acids or bases.

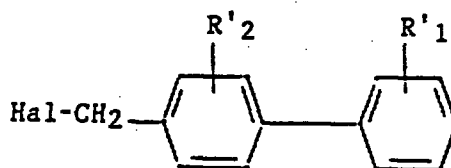
8. A method of preparing a compound (I) according to any one of claims 1 to 7, characterized in that:

a1) a heterocyclic derivative of the formula



2

in which z , t , R_3 , R_4 and R_5 are as defined for (I) in claim 1, is reacted with a (biphenyl-4-yl)methyl derivative of the formula

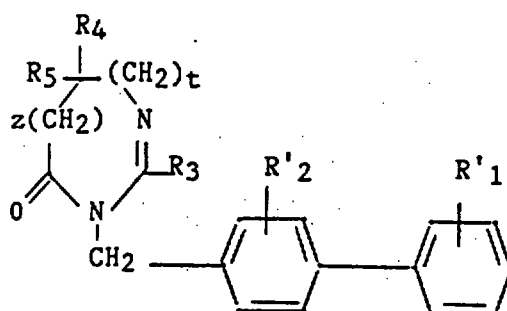


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in which Hal is a halogen atom and R'_1 and R'_2 are respectively either R_1 and R_2 or a precursor group of R_1 and R_2 ;

b1) if appropriate, the resulting compound of the formula

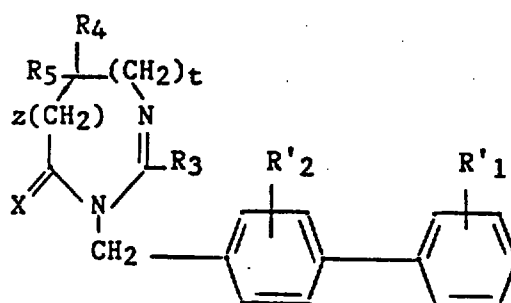




4

is treated with Lawesson's reagent [2,4-bis(4-methoxy-phenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide]; and

c1) the compound obtained in a1) or b1), of the formula

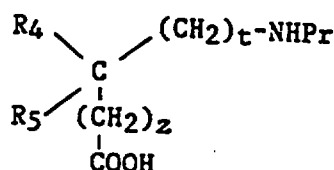


5

in which X is an oxygen atom or a sulfur atom, is treated to give the compound (I) by conversion of the groups R'1 and/or R'2 to the groups R1 and/or R2 respectively.

9. A method of preparing a compound (I) according to any one of claims 1 to 7, characterized in that

a2) an amino acid of the formula

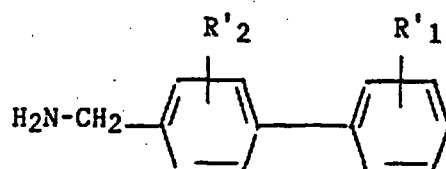


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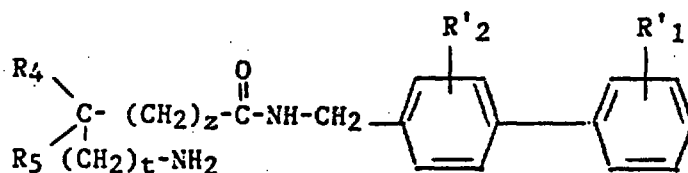
in which z , t , R_4 and R_5 are as defined for (I) in claim 1, and of which the amine group is protected by the Pr group, is reacted with a (biphenyl-4-yl)methylamine derivative of the formula



8

in which R'_1 and R'_2 are respectively either R_1 and R_2 or a precursor group of R_1 and R_2 ;

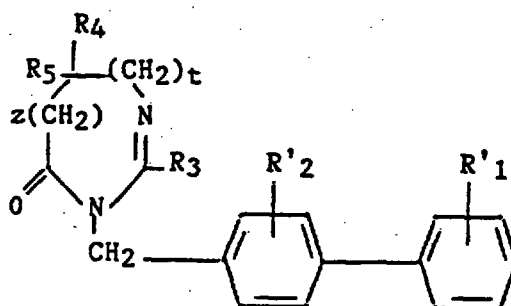
b2) after deprotection of the amine, the resulting compound of the formula



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is then treated with an alkyl ortho-ester of the formula $R_3C(OR)_3$ (10), in which R_3 is as defined for (I) in claim 1 and R is a C_1 - C_4 alkyl;

c2) if appropriate, the resulting compound of the formula



4

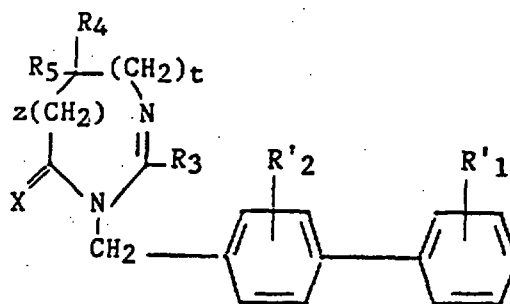
is treated with Lawesson's reagent [2,4-bis(4-methoxy-





phenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide];
and

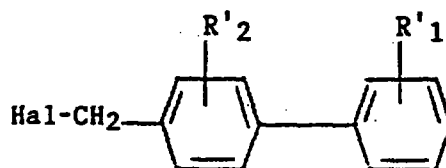
d2) the compound thus obtained in b2 or c2, of
the formula

5

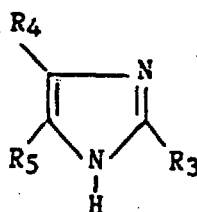
is then treated under suitable conditions for preparing
the compound (I) by conversion of the groups R'₂ and/or
R'₁ to the groups R₂ and/or R₁ respectively.

10. A method of preparing a compound (I) according to
claim 6, characterized in that

a3) a (biphenyl-4-yl)methyl derivative of the
formula

3

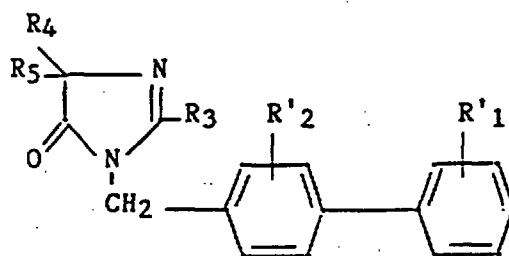
in which Hal is a halogen atom and R'₁ and R'₂ are res-
pectively either R₁ and R₂ or a precursor group of R₁
and R₂, is reacted with an imidazole derivative of the
formula

11



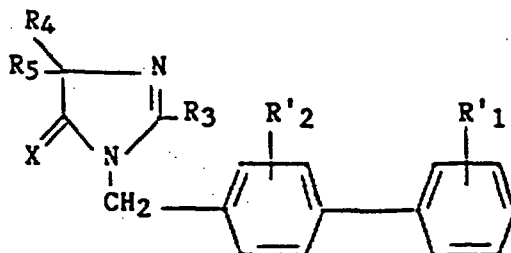
in which R_3 , R_4 and R_5 are as defined for (I) in claim 1, in the presence of oxygen and UV irradiation and in a basic medium;

b3) if appropriate, the resulting compound of the formula

4'

is treated with Lawesson's reagent [2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane 2,4-disulfide]; and

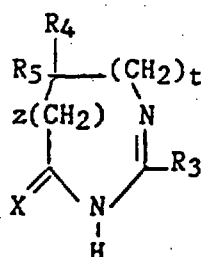
c3) the compound thus obtained in b3 or c3, of the formula

5'

is then treated under suitable conditions for preparing the compound (I) by conversion of the groups R'_1 and/or R'_2 to the groups R_1 and/or R_2 respectively.

11. A compound of the formula





(II)

in which:

- R_3 is a hydrogen, a C_1 - C_6 alkyl which is unsubstituted or substituted by one or more halogen atoms, a C_2 - C_6 alkenyl, a C_3 - C_7 cycloalkyl, a phenyl, a phenylalkyl in which the alkyl is C_1 - C_3 , or a phenylalkenyl in which the alkenyl is C_2 - C_3 , said phenyl groups being unsubstituted or monosubstituted or polysubstituted by a halogen atom, a C_1 - C_4 alkyl, a C_1 - C_4 halogenoalkyl, a C_1 - C_4 polyhalogenoalkyl, a hydroxyl or a C_1 - C_4 alkoxy;
- R_4 and R_5 are each independently a C_1 - C_6 alkyl, a phenyl or a phenylalkyl in which the alkyl is C_1 - C_3 , said alkyl, phenyl and phenylalkyl groups being unsubstituted or substituted by one or more halogen atoms or by a group selected from a C_1 - C_4 perfluoroalkyl, a hydroxyl and a C_1 - C_4 alkoxy;
- or R_4 and R_5 together form a group of the formula $=CR_7R_8$, in which R_7 is hydrogen, a C_1 - C_4 alkyl or a phenyl and R_8 is a C_1 - C_4 alkyl or a phenyl;
- or else R_4 and R_5 together are either a group of the formula $(CH_2)_n$ or a group of the formula $(CH_2)_pY(CH_2)_q$, in which Y is either an oxygen atom, or a sulfur atom, or a carbon atom substituted by a C_1 - C_4 alkyl group, a phenyl or a phenylalkyl in which the alkyl is C_1 - C_3 , or a group $N-R_6$, in which R_6 is a hydrogen, a C_1 - C_4 alkyl, a phenylalkyl in which the alkyl is C_1 - C_3 , a C_1 - C_4 alkylcarbonyl, a C_1 - C_4 halogenoalkylcarbonyl, a C_1 - C_4 polyhalogenoalkylcarbonyl,



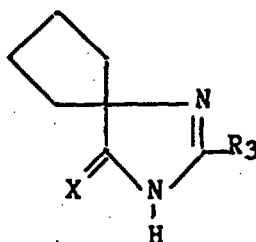


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a benzoyl, an alpha-aminoacyl or an N-protecting group, or R_4 and R_5 , together with the carbon atom to which they are bonded, form an indane or an adamantane;

- $p + q = m$;
 - n is an integer between 2 and 11;
 - m is an integer between 2 and 5;
 - X is an oxygen atom or sulfur atom; and
 - z and t are zero or one is zero and the other is one; with the limitation that
 - if z and t are zero and X is an oxygen atom, R_4 and R_5 are other than
 - a C_1-C_6 alkyl, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3 , said alkyl, phenyl and phenylalkyl groups being unsubstituted or substituted by one or more halogen atoms or by a group selected from a C_1-C_4 perfluoroalkyl, a hydroxyl and a C_1-C_4 alkoxy;
 - or R_4 and R_5 together are other than a group $N-R_6$ in which R_6 is a hydrogen, a C_1-C_4 alkyl or a phenylalkyl in which the alkyl is C_1-C_3 ; and
 - n is other than 6;
- and
- if $z = 1$ and R_3 is a phenyl, R_4 and R_5 are each other than a methyl.

12. A compound according to claim 11 of the formula



(II')

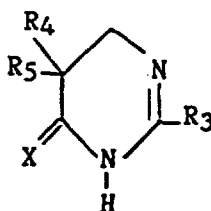
in which X is an oxygen atom or a sulfur atom and R_3 is





a hydrogen, a C_1-C_6 alkyl which is unsubstituted or substituted by one or more halogen atoms, a C_2-C_6 alkenyl, a C_3-C_7 cycloalkyl, a phenyl, a phenylalkyl in which the alkyl is C_1-C_4 , or a phenylalkenyl in which the alkenyl is C_2-C_3 , said phenyl groups being unsubstituted or monosubstituted or polysubstituted by a halogen atom, a C_1-C_4 alkyl, a C_1-C_4 halogenoalkyl, a C_1-C_4 polyhalogenoalkyl, a hydroxyl or a C_1-C_4 alkoxy.

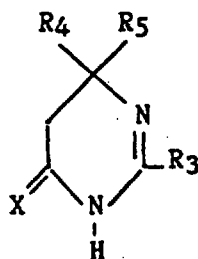
13. A compound according to claim 11 of the formula



(II'')

in which R_3 , R_4 , R_5 and X are as defined above for (II) in claim 10.

14. A compound according to claim 11 of the formula



(II''')

in which:

- R_3 is a hydrogen, a C_1-C_6 alkyl which is unsubstituted or substituted by one or more halogen atoms, a C_2-C_6 alkenyl, a C_3-C_7 cycloalkyl, a phenyl, a phenylalkyl in which the alkyl is C_1-C_3 , or a phenylalkenyl in which the alkenyl is C_2-C_3 , said phenyl groups being unsubstituted or monosubstituted or polysubstituted by a halogen atom, a C_1-C_4 alkyl, a





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C_1-C_4 halogenoalkyl, a C_1-C_4 polyhalogenoalkyl, a hydroxyl or a C_1-C_4 alkoxy;

- R_4 and R_5 are each independently a C_1-C_6 alkyl, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3 , said alkyl, phenyl and phenylalkyl groups being unsubstituted or substituted by one or more halogen atoms or by a group selected from a C_1-C_4 perfluoroalkyl, a hydroxyl and a C_1-C_4 alkoxy;
 - or R_4 and R_5 together form a group of the formula $=CR_7R_8$, in which R_7 is hydrogen, a C_1-C_4 alkyl or a phenyl and R_8 is a C_1-C_4 alkyl or a phenyl;
 - or R_4 and R_5 together are either a group of the formula $(CH_2)_n$ or a group of the formula $(CH_2)_pY(CH_2)_q$, in which Y is either an oxygen atom, or a sulfur atom, or a carbon atom substituted by a C_1-C_4 alkyl group, a phenyl or a phenylalkyl in which the alkyl is C_1-C_3 , or a group $N-R_6$, in which R_6 is a hydrogen, a C_1-C_4 alkyl, a phenylalkyl in which the alkyl is C_1-C_4 , a C_1-C_4 alkylcarbonyl, a C_1-C_4 halogenoalkylcarbonyl, a C_1-C_4 polyhalogenoalkylcarbonyl, a benzoyl, an alpha-aminoacyl or an N-protecting group, or R_4 and R_5 , together with the carbon atom to which they are bonded, form an indane or an adamantane;
 - $p + q = m$;
 - n is an integer between 2 and 11;
 - m is an integer between 2 and 5; and
 - X is an oxygen atom or a sulfur atom;
- with the limitation that R_3 is other than a phenyl if R_4 and R_5 are each a methyl.

15. A method of preparing a compound according to any one of claims 11 to 14, characterized in that it comprises reacting a compound of the formula

 R_3-B

14



* C L M S *



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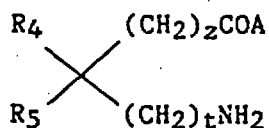
in which R_3 is as defined above for (II) in claim 10 and B is

- a group $C(OR)_3$

- a group $\begin{array}{c} \text{NH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{OR} \end{array}$ or

- a group $COHal$

R being a C_1 - C_4 alkyl and Hal denoting a halogen atom, preferably chlorine, with a compound of the formula

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in which R_4 and R_5 are as defined above for (II) in claim 10 and A is an OH group, an NH_2 group or a group OR' , R' being hydrogen or a C_1 - C_4 alkyl, and then, if appropriate, treating the resulting compound with Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane disulfide).

16. A pharmaceutical composition in which a compound according to any one of claims 1 to 7 is present as the active principle.

17. A pharmaceutical composition in which a compound according to any one of claims 1 to 7 is present in association with a beta-blocking compound.

18. A pharmaceutical composition in which a compound according to any one of claims 1 to 7 is present in association with a diuretic.

19. A pharmaceutical composition in which a compound according to any one of claims 1 to 7 is present in association with a non-steroidal antiinflammatory.

20. A pharmaceutical composition in which a compound according to any one of claims 1 to 7 is present in association with a calcium antagonist.



21. A pharmaceutical composition in which a compound according to any one of claims 1 to 7 is present in association with a tranquilizer.

This Sheet Has Been Replaced



* C L M S *