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(54) Title
New imidazolidines substituted by a heterocycle, their preparation process and intermediates, their use as medicaments and the pharmaceutical compositions containing them

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C07D 491/107	**C07D 233/88**
A61K 031/415	**C07D 471/10**
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(12) PATENT ABSTRACT (11) Document No. AU-A-32921/95
(19) AUSTRALIAN PATENT OFFICE

(54) Title
NEW IMIDAZOLIDINES SUBSTITUTED BY A HETEROCYCLE, THEIR PREPARATION PROCESS AND INTERMEDIATES, THEIR USE AS MEDICAMENTS AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

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(21) Application No. : **32921/95** (22) Application Date : **28.09.95**

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(72) Inventor(s)
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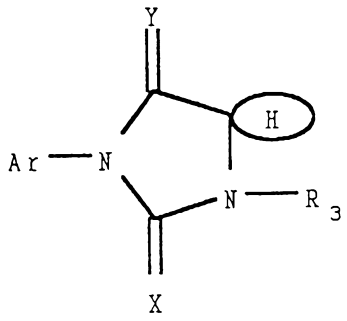
(57) Claim

1) Products of formula (I):



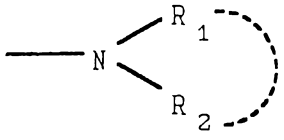
(I)

in which (H) represents a saturated heterocyclic radical with 4 to 7 members containing:
either an oxygen, nitrogen or sulphur atom, optionally oxidized, the nitrogen atom being optionally substituted by a radical chosen from the values of R_3,
or two oxygen atoms and optionally one boron atom substituted by a phenyl radical, the heterocycle thus formed being optionally substituted on a carbon atom by an oxo radical, by one or more alkyl radicals, themselves optionally substituted, or by a cycloalkyl radical containing 4 to 7 members,

.../2

Ar represents an aryl radical optionally substituted by one or more radicals chosen from:

i) halogen atoms and cyano, nitro, trifluoromethyl, trifluoromethoxy, hydroxyl, free, salified, esterified or amidified carboxy radicals,

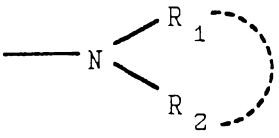
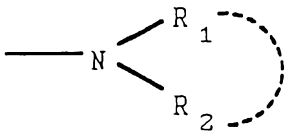
ii) the  radical

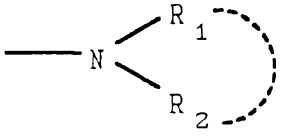
in which the nitrogen atom is optionally oxidized and R_1 and R_2:

either, identical or different, are chosen from the hydrogen atom and optionally substituted alkyl radicals,

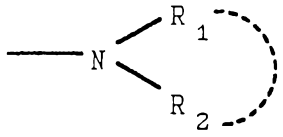
or form together with the nitrogen atom to which they are linked a monocyclic radical containing 5, 6 or 7 members or a radical constituted by condensed rings containing 8 to 14 members, these identical or different radicals optionally containing one or more other heteroatoms chosen from oxygen, nitrogen and sulphur atoms, and being optionally substituted,

iii) optionally substituted alkyl, alkoxy, alkylthio and arylthio,

iiii) alkyl  and alkoxy 

with  as defined above,

X represents an oxygen or sulphur atom,
Y represents an oxygen or sulphur atom or an NH radical
R_3 is chosen from the hydrogen atom, aryl radicals and alkyl, alkenyl and alkynyl radicals optionally interrupted by one or more oxygen, nitrogen or sulphur atoms, optionally oxidized, all these radicals being optionally substituted,
the substituent or substituents of the ring which can be constituted by



and alkyl, aryl, alkoxy, alkenyl and alkynyl radicals indicated above as optionally substituted, being chosen from halogen atoms and the following radicals: optionally salified, esterified or etherified hydroxy, alkoxy, aryloxy, alkyl, haloalkoxy, haloalkyl, mercapto, alkylthio and arylthio in which the sulphur atom is optionally oxidized, acyl, acyloxy, free, salified, esterified or amidified carboxy, cyano, nitro, amino, mono or dialkylamino, aryl and arylalkyl, these last two radicals being optionally substituted by one or more radicals chosen from halogen atoms, the following radicals: hydroxyl, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, free, salified or esterified carboxy and tetrazolyl, all the sulphur atoms being optionally oxidized into the sulphoxide or sulphone,
the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

8) As medicaments, the pharmaceutically acceptable products of formula (I) as defined in claims 1 to 3.

AUSTRALIA

PATENTS ACT 1990

COMPLETE SPECIFICATION

FOR A STANDARD PATENT

ORIGINAL

TO BE COMPLETED BY APPLICANT

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Invention Title: "NEW IMIDAZOLIDINES SUBSTITUTED BY A HETEROCYCLE, THEIR PREPARATION PROCESS AND INTERMEDIATES, THEIR USE AS MEDICAMENTS AND THE PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

The following statement is a full description of this invention, including the best method of performing it known to me:-

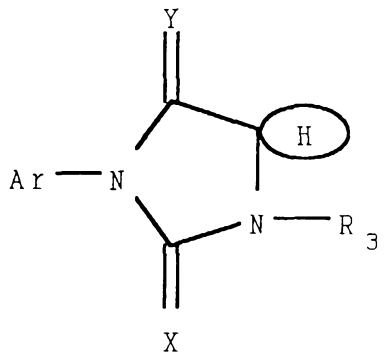
New imidazolidines substituted by a heterocycle, their preparation process and intermediates, their use as medicaments and the pharmaceutical compositions containing them.

The present invention relates to new imidazolidines substituted by a heterocycle, their preparation process and intermediates, their use as medicaments and the pharmaceutical compositions containing them.

In the Japanese Application J 48087030 3-phenyl 2-thiohydantoins are described which are presented as inhibiting the germination of certain plants.

In the French Patent 2,329,276 imidazolidines are described which are presented as possessing an antiandrogen activity. The products of this Patent are however different from the products of the present Patent Application.

Therefore a subject of the present invention is the products of formula (I):



(I)

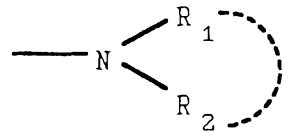
in which (H) represents a saturated heterocyclic radical with 4 to 7 members containing:

either an oxygen, nitrogen or sulphur atom, optionally oxidized, the nitrogen atom being optionally substituted by a radical chosen from the values of R_3,

or two oxygen atoms and optionally one boron atom substituted by a phenyl radical, the heterocycle thus formed being optionally substituted on a carbon atom by an oxo radical, by one or more alkyl radicals, themselves optionally substituted, or by a cycloalkyl radical containing 4 to 7 members,

Ar represents an aryl radical optionally substituted by one or more radicals chosen from:

i) halogen atoms and cyano, nitro, trifluoromethyl, trifluoromethoxy, hydroxyl, free, salified, esterified or amidified carboxy radicals,

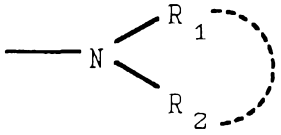
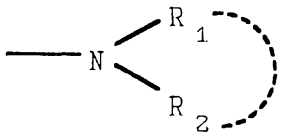
ii) the radical 

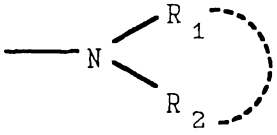
in which the nitrogen atom is optionally oxidized and R_1 and R_2:

either, identical or different, are chosen from the hydrogen atom and optionally substituted alkyl radicals,

or form together with the nitrogen atom to which they are linked a monocyclic radical containing 5, 6 or 7 members or a radical constituted by condensed rings containing 8 to 14 members, these identical or different radicals optionally containing one or more other heteroatoms chosen from oxygen, nitrogen and sulphur atoms, and being optionally substituted,

iii) optionally substituted alkyl, alkoxy, alkylthio and arylthio,

iiii) alkyl  and alkoxy 

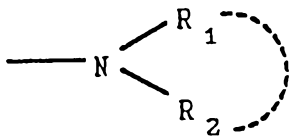
with  as defined above,

X represents an oxygen or sulphur atom,

Y represents an oxygen or sulphur atom or an NH radical

R_3 is chosen from the hydrogen atom, aryl radicals and alkyl,

alkenyl and alkynyl radicals optionally interrupted by one or more oxygen, nitrogen or sulphur atoms, optionally oxidized, all these radicals being optionally substituted, the substituent or substituents of the ring which can be constituted by



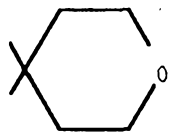
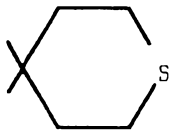
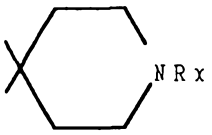
and alkyl, aryl, alkoxy, alkenyl and alkynyl radicals indicated above as optionally substituted, being chosen from halogen atoms and the following radicals: optionally salified, esterified or etherified hydroxy, alkoxy, aryloxy, alkyl, haloalkoxy, haloalkyl, mercapto, alkylthio and arylthio in which the sulphur atom is optionally oxidized, acyl, acyloxy, free, salified, esterified or amidified carboxy, cyano, nitro, amino, mono or dialkylamino, aryl and arylalkyl, these last two radicals being optionally substituted by one or more radicals chosen from halogen atoms, the following radicals: hydroxyl, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, free, salified or esterified carboxy and tetrazolyl, all the sulphur atoms being optionally oxidized into the sulphoxide or sulphone, the following products to be excluded:
3-phenyl-8-(phenylmethyl) -1, 3, 8-Triazaspiro (4,5) decan-2, 4-dione;
3-phenyl-8-propyl-1, 3, 8-Triazaspiro (4,5) decan-2, 4-dione;
8-butyl-3-phenyl-1, 3, 8-Triazaspiro (4,5) decan-2, 4-dione;
8-isopropyl-3-phenyl-1, 3, 8-Triazaspiro (4,5) decan-2, 4-dione;
8-butyl-1, 3-diphenyl-1, 3, 8-Triazaspiro (4,5) decan-2, 4-dione;
the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

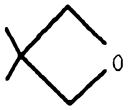
For the definition of the substituents indicated above and in what follows, the definitions used can have the following values:
the heterocyclic radical which is represented by (H) can be chosen from the radicals of the saturated heterocycles as defined above, known to a man skilled in the art.

There can be mentioned by way of example and in a non-

exhaustive manner:

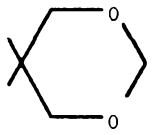
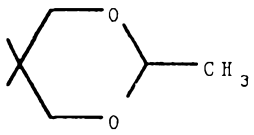
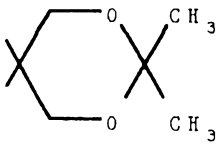
- on the one hand, the radicals containing an oxygen, nitrogen or sulphur atom such as in particular the following radicals:

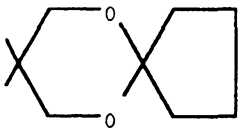
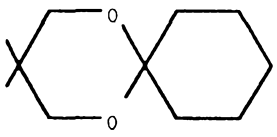
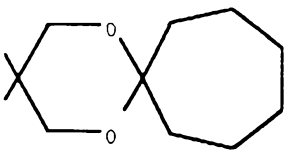




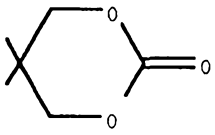
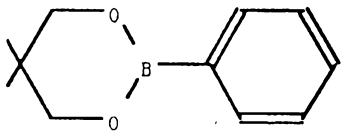


in which Rx is chosen from the values of R_3 as defined above and in particular the hydrogen atom and the alkyl radicals optionally interrupted by one or more oxygen, nitrogen or sulphur atoms, optionally oxidized, the alkyl radicals being optionally substituted as defined above and hereafter,

- on the other hand, the radicals containing two oxygen atoms and optionally one boron atom such as in particular the following radicals:

The heterocyclic radical (H) preferably contains 6 members.

The term alkyl designates a linear or branched alkyl radical, having at most 12 carbon atoms, such as for example the following radicals: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, sec-pentyl, tert-pentyl, neo-pentyl, hexyl, isohexyl, sec-hexyl, tert-hexyl, heptyl, octyl, decyl, undecyl, dodecyl.

The alkyl radicals having at most 4 carbon atoms are preferred and in particular the methyl, ethyl, propyl, isopropyl radicals.

The term alkenyl designates a linear or branched alkenyl radical having at most 12 carbon atoms such as for example the vinyl, allyl, 1-propenyl, butenyl, pentenyl, hexenyl radicals.

Among the alkenyl radicals, those with 4 carbon atoms are preferred such as the allyl, propenyl or butenyl radicals.

The term alkynyl designates a linear or branched alkynyl radical having at most 12 carbon atoms, such as for example the ethynyl, propargyl, butynyl, pentynyl or hexynyl radicals.

Among the alkynyl radicals, those with 4 carbon atoms are preferred such as the propargyl radical.

The term alkoxy designates a linear or branched radical containing at most 12 and preferably 4 carbon atoms such as preferably the methoxy, ethoxy, propoxy or isopropoxy radicals, but also a linear, secondary or tertiary butoxy radical.

The term cycloalkyl radical preferably designates cyclopropyl, cyclobutyl radicals and quite particularly cyclopentyl, cyclohexyl and cycloheptyl radicals.

By aryl is meant the carbocyclic aryl radicals such as phenyl or naphthyl or the monocyclic heterocyclic aryls with 5 or 6 members or constituted by condensed rings, containing one or more heteroatoms preferably chosen from oxygen, sulphur and nitrogen.

Among the heterocyclic aryls with 5 members the

following radicals can be mentioned: furyl, thienyl, pyrrolyl, thiazolyl, oxazolyl, imidazolyl, thiadiazolyl, pyrazolyl, isoxazolyl, tetrazolyl.

Among the heterocyclic aryls with 6 members the following radicals can be mentioned: pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl.

Among the condensed aryl radicals there can be mentioned the indolyl, benzofurannyl, benzothienyl, quinolinyl radicals.

The phenyl, tetrazolyl and pyridyl radicals are preferred.

By arylalkyl is meant the radicals resulting from the combination of the alkyl radicals and the aryl radicals mentioned above.

The benzyl, phenylethyl, pyridylmethyl, pyridylethyl or tetrazolylmethyl radicals are preferred.

By halogen is meant of course the fluorine, chlorine, bromine or iodine atoms.

The fluorine, chlorine or bromine atoms are preferred.

As particular examples of alkyl radicals substituted by one or more halogens or haloalkyl, the following radicals can be mentioned: monofluoro-, chloro-, bromo- or iodomethyl or -ethyl, difluoro-, dichloro- or dibromomethyl, trifluoromethyl.

As particular examples of alkoxy radicals substituted by one or more halogens or haloalkoxy, the bromoethoxy, trifluoromethoxy, trifluoroethoxy or also pentafluoroethoxy radicals can be mentioned.

As particular examples of substituted aryl or aralkyl radicals, there can be mentioned in a non-exhaustive manner those in which the phenyl radical is substituted in ortho, meta or para position by one or more radicals chosen from the fluorine atom and alkylthio, hydroxy, hydroxyalkyl, alkoxy, trifluoromethyl, trifluoroethyl, pentafluoroethyl and cyano radicals.

By acyl radical is preferably meant a radical having at most 7 carbon atoms such as the formyl, acetyl, propionyl, butyryl or benzoyl radical, but it can also represent a

valeryl, hexanoyl, acryloyl, crotonoyl or carbamoyl radical.

By acyloxy radical is meant the radicals in which the acyl radicals have the meaning indicated above and for example the formyloxy, acetoxy, propionyloxy, butyryloxy or benzoyloxy radicals.

- The term aryloxy radical preferably designates the radicals in which the aryl radical is as defined above such as for example in phenoxy,
- the term arylalkoxy radical preferably designates the radicals in which the aryl radical and the alkoxy radical represent the radicals as defined above such as for example in benzyloxy, phenylethoxy or phenylisopropoxy,
- the term arylthio radical preferably designates the radicals in which the aryl radical represents the radicals as defined above such as for example in phenylthio, pyridylthio or pyrimidylthio, imidazolylthio or N-methylimidazolylthio,
- the term alkylthio radical preferably designates the radicals in which the alkyl radical is as defined above such as for example in methylthio, ethylthio, propylthio, isopropylthio, butylthio, sec-butylthio, tert-butylthio, isopentylthio or isohexylthio; the alkylthio radical is optionally substituted such as for example in hydroxymethylthio, aminoethylthio, haloalkylthio such as preferably bromoethylthio, trifluoromethylthio, trifluoroethylthio or also pentafluoroethylthio, arylalkylthio such as for example benzylthio or phenethylthio.

The sulphur atoms can be non-oxidized as in the alkylthio, arylthio radicals or on the contrary be oxidized to give the alkylsulphinyl, arylsulphinyl, alkylsulphonyl, or arylsulphonyl radicals:

alkylsulphinyl and alkylsulphonyl designate the radicals in which the alkyl radical is chosen for example from the values indicated above for the alkyl radical such as for example the methylsulphinyl, ethylsulphinyl, methylsulphonyl or ethylsulphonyl radicals,

arylsulphinyl and arylsulphonyl designates the arylthio radicals in which the aryl radical is chosen, for example, from the values indicated above for the aryl radical such as

for example the following radicals: phenyl-sulphinyl or -sulphonyl, pyridyl-sulphinyl or -sulphonyl, pyrimidyl-sulphinyl or -sulphonyl, imidazolyl-sulphinyl or -sulphonyl or N-methylimidazolyl-sulphinyl or -sulphonyl.

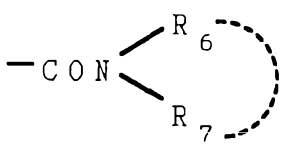
The carboxy radical or radicals of the products of formula (I) can be salified, amidified or esterified by the various groups known to a man skilled in the art.

By esterified carboxy is meant for example the alkyloxy-carbonyl radicals such as for example the methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, n-butyl, tert-butyloxy-carbonyl, or also benzyloxycarbonyl radicals, these alkyl radicals being able to be substituted by one or more radicals chosen for example from halogen atoms, hydroxyl, alkoxy, acyl, acyloxy, alkylthio, amino or aryl radicals such as, for example, in the chloromethyl, hydroxypropyl, propionyloxy-methyl, methylthiomethyl, dimethylaminoethyl, benzyl or phenethyl groups.

There can be mentioned the radicals formed with easily cleavable ester remainders such as the methoxymethyl, ethoxymethyl radicals; the acyloxyalkyl radicals such as pivaloyloxymethyl, pivaloyloxyethyl, acetoxymethyl or acetoxyethyl; the alkyloxycarbonyloxy alkyl radicals such as the methoxycarbonyloxy methyl or ethyl radicals, the isopropyloxycarbonyloxy methyl or ethyl radicals.

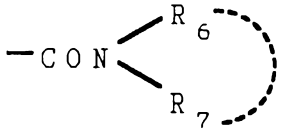
A list of such ester radicals can be found for example in the European Patent EP 0,034,536.

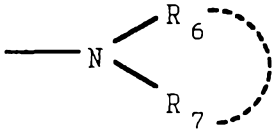
By amidified carboxy is meant the groups of the type



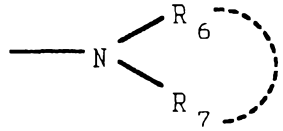
in which the radicals R_6 and R_7, identical or different, represent a hydrogen atom or an alkyl radical having 1 to 4 carbon atoms such as the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl or tert-butyl radicals.

In the

 groups defined above, those in which the

 radical represents the amino, mono- or

dimethylamino, mono- or diethylamino, methylethylamino, monopropylamino or monobutylamino radical are preferred.

The  radical can also represents a

heterocycle which may or may not contain an additional heteroatom. The pyrrolyl, imidazolyl, indolyl, piperidino, morpholino, piperazinyl radicals can be mentioned. The piperidino, morpholino or piperazinyl radicals optionally substituted on the second nitrogen atom are preferred, such as for example in methylpiperazinyl, fluoromethylpiperazinyl, ethylpiperazinyl, propylpiperazinyl, phenylpiperazinyl or benzylpiperazinyl: in these last two radicals, the phenyl and benzyl radicals can be substituted, such as for example in chlorophenyl or trifluorophenyl.

By salified carboxy is meant the salts formed for example with an equivalent of sodium, potassium, lithium, calcium, magnesium or ammonium. There can also be mentioned the salts formed with the organic bases such as methylamine, propylamine, trimethylamine, diethylamine, triethylamine, N,N-dimethylethanolamine, tris (hydroxymethyl) amino methane, ethanolamine, pyridine, picoline, dicyclohexylamine, morpholine, benzylamine, procaine, lysine, arginine,

histidine, N-methylglucamine.

The sodium salt is preferred.

By heterocyclic radical containing one or more heteroatoms is meant for example the saturated monocyclic heterocyclic radicals such as the following radicals: oxirannyl, oxolannyl, dioxolannyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl or morpholinyl.

By alkyl, alkenyl, or alkynyl optionally interrupted by a heteroatom chosen from sulphur, oxygen or nitrogen atoms is meant the radicals containing one or more of these atoms, identical or different in their structure, these heteroatoms obviously not being able to be situated at the end of the radical. There can be mentioned for example the alkoxyalkyl radicals such as methoxymethyl, methoxyethyl or propyloxypropyl, the alkoxyalkoxyalkyl radicals such as methoxyethoxymethyl or also the alkylthioalkyl radicals such as for example propylthiopropyl, propylthioethyl, methylthiomethyl.

By esterified, etherified or protected hydroxyl radical is meant the $-O-\overset{\overset{O}{\|}}{C}-\alpha_1$, $\alpha_2-O-\alpha_3$ or $-O-P$ radicals respectively,

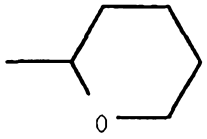
formed from a hydroxyl radical, according to the usual methods known to a man skilled in the art and in which P represents a protective group,

α_1, α_2 and α_3 represent an alkyl, alkenyl, alkynyl, aryl or arylalkyl radical, having at most 12 carbon atoms and optionally substituted as defined above in particular for R_3.

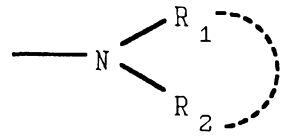
Examples of protective group P, as well as the formation of the protected hydroxyl radical, are given in particular in the standard book of a man skilled in the art: Protective Groups in Organic Synthesis, Theodora W. Greene, Harvard University, published in 1981 by Wiley-Interscience Publishers, John Wiley & Sons.

The protection group of the hydroxyl radical which can be represented by P can be chosen from the following list: for example formyl, acetyl, chloroacetyl, bromoacetyl, dichloroacetyl, trichloroacetyl, trifluoroacetyl,

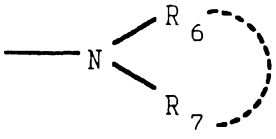
methoxyacetyl, phenoxyacetyl, benzoyl, benzoylformyl, p-nitrobenzoyl. The following groups can also be mentioned: ethoxycarbonyl, methoxycarbonyl, propoxycarbonyl, ßßß-trichloro-ethoxycarbonyl, benzyloxycarbonyl, tert-butoxy-carbonyl, 1-cyclo propylethoxycarbonyl, tetrahydro-pyrannyl, tetrahydrothiopyrannyl, methoxytetrahydropyrannyl, trityl, benzyl, 4-methoxybenzyl, benzhydryl, trichloroethyl, 1-methyl 1-methoxyethyl, phthaloyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, oxalyl, succinyl and pivaloyl, phenylacetyl, phenylpropionyl, mesyl, chlorobenzoyl, para-nitrobenzoyl, para-tert-butylbenzoyl, caprylyl, acryloyl, methylcarbamoyl, phenylcarbamoyl, naphthylcarbamoyl.
P can in particular represent the

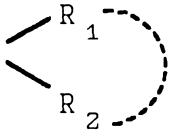


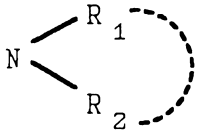
radical or also a silicon derivative such as trimethylsilyl.

The 

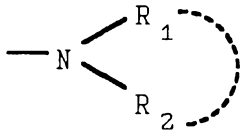
radical which represents an amino, monoalkylamino, dialkyl-amino radical or also a heterocycle can be chosen from the values defined above for



The -alkyl— 

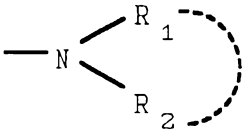
and -alkoxy— 

radicals are such that in these radicals, alkyl, alkoxy and



have the values indicated above, suche as

for example in the NN-dimethylaminomethyl or NN-dimethyl-aminomethoxy radicals.

The amino radical and in particular 

also designates the amino radical substituted by one or two alkyl radicals chosen from the alkyl radicals as defined above themselves substituted as indicated above in particular by one or more radicals chosen from halogen atoms and the hydroxy, alkoxy, cyano, free, salified, esterified or amidified carboxy radicals, such as for example the hydroxyalkyl, cyanoalkyl and carboxyalkyl radicals.

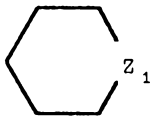
When the products of formula (I) as defined above contain an amino radical salifiable by an acid it is understood that these acid salts are also a subject of the invention.

The addition salts with mineral or organic acids of the products of formula (I) can be, for example, the salts formed with the following acids: hydrochloric, hydrobromic, hydroiodic, nitric, sulphuric, phosphoric, propionic, acetic, formic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic, ascorbic, alkylmonosulphonic such as for example methanesulphonic, ethanesulphonic, propanesulphonic, alkyldisulphonic such as for example methanedisulphonic, alpha, beta-ethanedisulphonic, arylmonosulphonic such as benzenesulphonic and aryl-disulphonic.

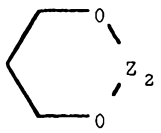
There can be mentioned more particularly the salts

formed with hydrochloric or methanesulphonic acids for example.

A particular subject of the invention is the products of formula (I) as defined above, in which (H) represents

either the  radical

in which Z_1 represents an oxygen atom, a sulphur atom optionally oxidized in the form of the sulphoxide or sulphone or an $-N-R_4$ radical in which R_4 is chosen from the hydrogen atom and alkyl, alkylphenyl and phenyl radicals optionally substituted by one or more radicals chosen from halogen atoms and hydroxy, alkoxy, free, salified, esterified or amidified carboxy radicals and the phenyl radical itself optionally substituted by one or more radicals chosen from halogen atoms, hydroxyl, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano and free, salified or esterified carboxy radicals

or the  radical

in which Z_2 represents either a $-CH_2-$ radical optionally substituted by one or two alkyl radicals, a cycloalkyl radical or an oxo radical containing 4 to 7 members, or a boron atom substituted by a phenyl radical,
Ar represents an aryl radical optionally substituted by one or more radicals chosen from halogen atoms and the following radicals: cyano, nitro, trifluoromethyl, trifluoromethoxy, hydroxyl, free, salified, esterified or amidified carboxy, alkyl, alkoxy, alkylthio, arylthio, amino, mono or dialkylamino, aminoalkyl, mono or dialkylaminoalkyl, aminoalkoxy, mono or dialkylaminoalkoxy, pyrrolidinyl,

piperidyl, morpholino and piperazinyl optionally substituted on the second nitrogen atom by an alkyl, phenylalkyl, alkylphenyl or phenyl radical, themselves optionally substituted by one or more radicals chosen from halogen atoms and the hydroxyl and alkoxy radicals,

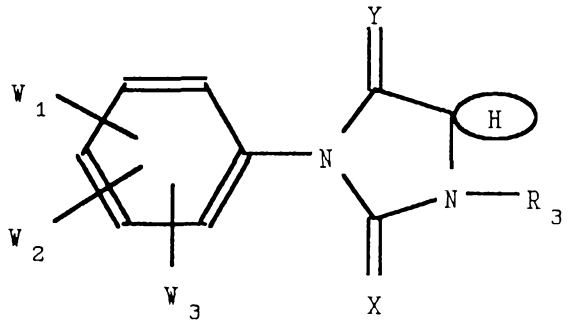
X represents an oxygen or sulphur atom,

Y represents an oxygen or sulphur atom or an NH radical,

R_3 is chosen from the hydrogen atom, aryl radicals and alkyl, alkenyl and alkynyl radicals optionally interrupted by one or more oxygen, nitrogen or sulphur atoms, optionally oxidized, all these radicals being optionally substituted by one or more radicals chosen from the halogen atoms and the following radicals: optionally salified, esterified or etherified hydroxy, alkoxy, aryloxy, alkyl, trifluoromethyl, trifluoromethoxy, free, salified, esterified or amidified carboxy, cyano, nitro, amino, mono or dialkylamino, phenyl, benzyl and phenethyl themselves optionally substituted by one or more radicals chosen from the halogen atoms and hydroxyl, alkyl, alkoxy, cyano, nitro and trifluoromethyl radicals, the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

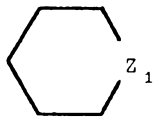
Among these products, a particular subject of the invention is the products of formula (I) as defined above, in which Ar represents a phenyl or pyridyl radical optionally substituted as indicated above and (H), R_3, X and Y have the meanings indicated above, the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

Among these products, a more particular subject of the invention is the products of formula (I) as defined above, and corresponding to formula (F):

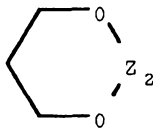


(F)

in which (H) represents:

either the  radical

in which Z_1 represents an oxygen atom, a sulphur atom optionally oxidized in the form of the sulphoxide or sulphone or an $-N-R_4$ in which R_4 is chosen from the hydrogen atom and alkyl radicals, optionally substituted by one or more radicals chosen from halogen atoms and hydroxy, alkoxy and free, salified, esterified or amidified carboxy radicals

or the  radical

in which Z_2 represents either a $-CH_2-$ radical optionally substituted by one or two alkyl radicals, a cycloalkyl radical or an oxo radical containing 4 to 7 members, or a boron atom substituted by a phenyl radical,

W_1, W_2 and W_3, identical or different, are chosen from the hydrogen atom, halogen atoms and the following radicals: hydroxyl, alkoxy, cyano, amino, mono or dialkylamino, nitro, trifluoromethyl, free, esterified, amidified or salified carboxy, alkylthio and arylthio,

R_3 is chosen from the hydrogen atom and alkyl radicals, optionally substituted by one or more substituents chosen from halogen atoms and optionally salified or etherified

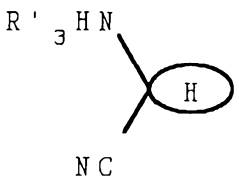
hydroxy radicals, alkoxy radicals and free, esterified, amidified or salified carboxy radicals,
X represents an oxygen or sulphur atom,
Y represents an oxygen atom or an NH radical,
the said products of formula (F) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (F).

Among the preferred products of the invention, there can be mentioned more particularly the products of formula (I) as defined above the names of which follow:
- 4-(2,4-dioxo 1-(4-hydroxybutyl) 8-oxa 1,3-diazaspiro (4.5)decan 3-yl) 2-(trifluoromethyl) benzonitrile,
- 4-(2,4-dioxo 1-(2-fluoroethyl) 8-oxa 1,3-diazaspiro (4.5)decan 3-yl) 2-(trifluoromethyl) benzonitrile,
- 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 8-oxa 1,3-diazaspiro (4.5)decane 1-acetonitrile,
- 4-(2,4-dioxo 1-(4-hydroxybutyl) 8-thia 1,3-diazaspiro (4.5)decan 3-yl) 2-(trifluoromethyl) benzonitrile.

Also a subject of the invention is a preparation process for products of formula (I) as defined above, characterized in that a product of formula (II):

$$Ar\text{-}N{=}C{=}X \qquad (II)$$

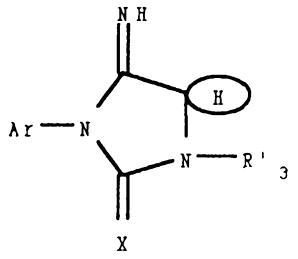
in which X has the meaning indicated above and Ar has the meaning indicated above, in which the optional reactive functions are optionally protected, is reacted, in the presence of a tertiary base,
either with a product of formula (III):



(III)

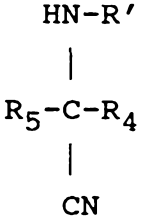
in which (H) has the meaning indicated above and R'_3 has the meaning indicated above for R_3 in which the optional reactive

functions are optionally protected, in order to obtain a product of formula (Ia):



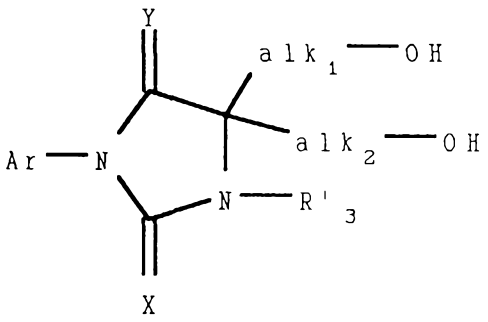
(Ia)

in which Ar, (H) and R'_3 have the meanings indicated above, or with a product of formula (X):



(X)

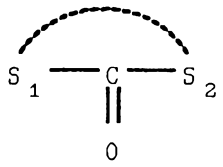
in which R'_3 has the meaning indicated above and R_4 and R_5, identical or different, represent a hydroxyalkyl radical in which the hydroxy function is optionally protected, in order to obtain, if appropriate after deprotection of the hydroxyl radicals, a diol of formula (IV):



(IV)

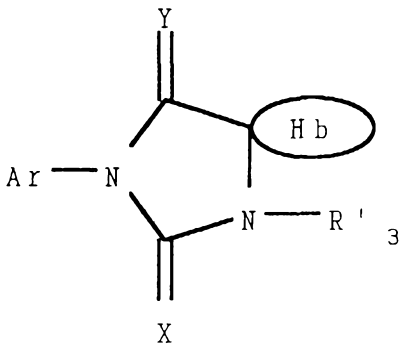
in which Ar, X and R'_3 have the meanings indicated above, Y has the meaning indicated above and alk_1 and alk_2, identical or different, represent an alkyl radical, which product of formula (IV) is reacted:

either with a compound of formula (V):



(V)

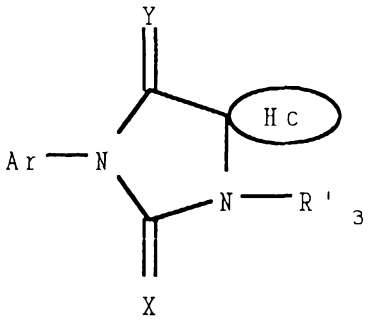
in which S_1 and S_2, identical or different, represent a hydrogen atom or an alkyl radical, optionally substituted, or S_1 and S_2 form together with C=O a cycloalkanone radical containing 4 to 7 members, in order to obtain a product of formula (Ib):



(Ib)

in which (Hb) represents a saturated heterocycle with 4 to 7 members containing two oxygen atoms and optionally substituted by a cycloalkyl radical or by one or two alkyl radicals themselves optionally substituted,

or with phosgene or a derivative of phosgene or N,N'-carbonyldiimidazole, in order to obtain the product of formula (Ic):



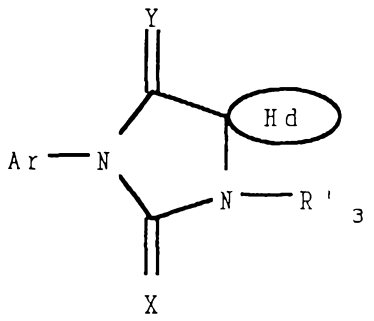
(Ic)

in which Ar, Y, X and R'_3 have the meanings indicated above and (Hc) represents a saturated heterocycle with 4 to 7 members, containing two oxygen atoms and substituted on a carbon atom by an oxo radical,

or with the compound of formula (VI):

$R\text{-}B(OH)_2$ (VI)

in which R represents a phenyl radical, in order to obtain the product of formula (Id):



(Id)

in which Ar, Y, X and R'_3 have the meanings indicated above and (Hd) represents a saturated heterocycle with 4 to 7 members, containing two oxygen atoms and one boron atom substituted by a phenyl radical,

the hydroxyl radicals of which product of formula (IV) can if desired and if necessary be protected in order to obtain a product of formula (IV'),

- which products of formulae (Ia), (Ib), (Ic), (Id) and (IV') thus obtained, as defined above, if appropriate, and if necessary or if desired, can be subjected to any one or more of the following reactions, in any order:

a) elimination reaction of the optional protective groups which can be carried by R'_3, then if appropriate the action of an esterification, amidification or salification agent,

b) hydrolysis reaction of the >C=NH group into a carbonyl function,

c) conversion of the >C=O group into a >C=S group,

d) conversion of the >C=S group or groups into a >C=O group,

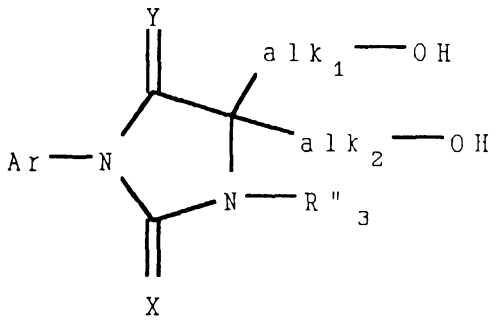
e) when R'_3 represents an alkoxyalkyl radical, conversion reaction of R'_3 into a hydroxyalkyl radical,

f) when R'_3 represents a hydrogen atom, the action of a reagent of formula Hal-R''_3 in which R''_3 has the values of R'_3 with the exception of the hydrogen value and Hal represents a halogen atom, in order to obtain products of formulae (Ia), (Ib), (Ic), (Id) and (IV') as defined above, in which R''_3 has

the meaning indicated previously,

g) if desired, the action on the products obtained in f, of an elimination agent of the optional protective groups which can be carried by R''_3 or if appropriate, the action of an esterification, amidification or salification agent,

- which products of formulae (Ib) and (IV') as defined above can be subjected to the reaction indicated above in f) then hydrolyzed into a product of formula (VII):



(VII)

in which Ar, X, Y, alk_1, alk_2 and R''_3 have the meanings indicated above,

which can be subjected to the same reactions as the product of formula (IV) as defined above, in order to obtain the corresponding products of formula (Ib), (Ic) or (Id) in which R''_3 has the meaning indicated above,

- which products of formulae (Ia), (IV), (IV'), (VII), (Ib), (Ic) and (Id) as defined above, if appropriate, and if necessary or if desired, can be subjected to any one or more of the following reactions, in any order:

- salification reaction by a mineral or organic acid or by a base in order to obtain the corresponding salt,

- elimination reaction of the optional protective groups which can be carried by the protected reactive functions.

The action of the products of formula (II) with the products of formula (III) or (X) is preferably carried out in an organic solvent such as tetrahydrofuran or dichloroethane but ethyl ether or isopropyl ether can also be used.

The operation is carried out in the presence of a tertiary base such as triethylamine or also pyridine or methylethylpyridine.

The reaction of the product of formula (IV) as defined

above with a compound of formula (V) as defined above to give a product of formula (Ib) as defined above, can be carried out according to the usual conditions known to a man skilled in the art and in particular as indicated in the book by Theodora W. Greene "Protection Group in Organic Synthesis" whose reference is given above.

When S_1 and S_2 both represent a hydrogen atom, the reaction is in particular described in the publication L. Hough J. K. N. Jones and M. S. Magson, J. Chem. Soc., 1525 (1952).

One of the S_1 and S_2 radicals can in particular represent a hydrogen atom or a methyl or tert-butyl radical and the other can in particular represent a methyl radical.

The S_1 and S_2 radicals can also form with C=O a cycloalkanone radical such as in particular cyclopentanone, cyclohexanone or cycloheptanone. The reaction of such compounds of formula (V) with the product of formula (IV) as defined above is in particular described in the publication W. A. R. van Heeswijk, J. B. Goedhart and J. F. G. Vliegenthart, Carbohydr. Res. 58, 337 (1977).

The obtaining of the product of formula (Ic) as defined above from the product of formula (IV) as defined above, can be carried out by reaction with phosgene or a derivative such as in particular triphosgene or also NN'-carbonyldiimidazole, as described for example in the publications W. N. Haworth and C. R. Porter, J. Chem. Soc. 151 (1930); R. L. Letsinger and K. K. Ogilvie, J. Org. Chem. 32, 296 (1967); J. P. Kutney and A. H. Ratcliffe, Synth. Common. 5, 47 (1975).

The obtaining of the product of formula (Id) as defined above by reaction of the product of formula (IV) with the product of formula (VI) can be carried out as indicated in particular in the publication R. J. Ferrier, Methods Carbohydr. Chem. VI, 419-426 (1972).

The two hydroxyl radicals of the product of formula (IV) as defined above can be protected in order to obtain the product of formula (IV') as defined above, in particular by the action of dihydropyran or a chlorosilane such as for example terbutyldimethylsilyl chloride.

The optional reactive functions which can be contained by R_3 and which are optionally protected, are hydroxy or amino functions. The usual protective groups are used to protect these functions. There can be mentioned for example the following protective groups of the amino radical: tert-butyl, tert-amyl, trichloroacetyl, chloroacetyl, benzhydryl, trityl, formyl, benzyloxycarbonyl.

As a protective group of the hydroxy radical there can be mentioned the radicals such as formyl, chloroacetyl, tetrahydropyrannyl, trimethylsilyl, tert-butyl dimethylsilyl.

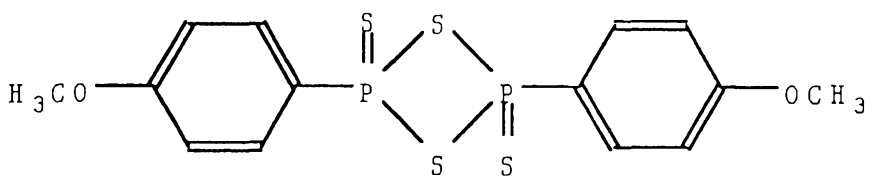
It is understood that the above list is not limitative and that other protective groups, for example known in the chemistry of the peptides, can be used. A list of such protective groups is found for example in the French Patent BF 2,499,995 the content of which is incorporated here by way of reference.

The optional elimination reactions of the protective groups are carried out as indicated in the said Patent BF 2,499,995. The preferred method of elimination is acid hydrolysis using acids chosen from hydrochloric, benzene sulphonic or para toluene sulphonic, formic or trifluoro-acetic acids. Hydrochloric acid is preferred.

The optional hydrolysis reaction of the >C=NH group into a ketone group is also preferably carried out using an acid such as aqueous hydrochloric acid for example under reflux.

When the hydrolysis of the >C=NH group into a carbonyl group is carried out on a molecule also containing a >C=S group, this can be converted into a >C=O group. The free OH radical which can optionally be contained by R_3 can then be converted into an SH radical.

The conversion reaction of the >C=O group or groups into a >C=S group is carried out using a so-called Lawesson reagent of formula:



which is a product marketed for example by the FLUKA company and the use of which is described for example in the publication: Bull. Soc. Chim. Belg. Vol. 87, No. 3, (1987) p. 229.

When it is desired to convert two >C=O functions into two >C=S functions the operation is carried out in the presence of an excess of Lawesson reagent. This is also the case when one starts with a molecule containing a >C=S function and a >C=O function and it is desired to convert said >C=O function into a >C=S function.

On the other hand when one starts with a molecule containing two >C=O functions and it is desired to obtain a product containing only one >C=S function, the operation is carried out in the presence of a deficit of Lawesson reagent. A mixture of three products is then generally obtained: each of the two products containing a >C=O function and a >C=S function and the product containing two >C=S functions. These products can then be separated by the usual methods such as chromatography.

The action on the product of formula (Ia), (Ib), (Ic), (Id) or (IV') of the reagent of formula Hal-R''_3 is carried out in the presence of a strong base such as sodium or potassium hydride. The operation can be carried out by phase transfer reaction in the presence of quaternary ammonium salts such as tert-butyl ammonium.

- The protective groups which can be carried by the substituent R''_3 can be for example one of those previously mentioned for R_3. The elimination reactions of the protective groups is carried out under the conditions indicated above.

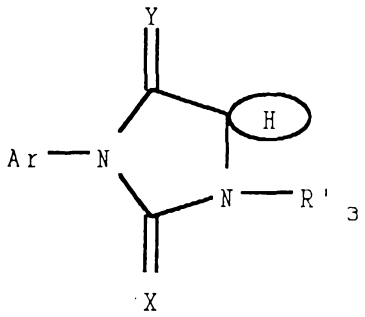
The elimination of the terbutyldimethylsilyl group can be carried out for example using hydrochloric acid.

- The optional esterification of the products of formula (I), as defined above, in which R''_3 contains a free OH radical is carried out under standard conditions. There can be used for example an acid or a functional derivative, for example an anhydride such as acetic anhydride in the presence of a base such as pyridine.

The optional esterification or salification of the products of formula (I) as defined above, in which R''_3 represents a COOH group, is carried out under standard conditions known to a man skilled in the art.

- The optional amidification of the products of formula (I), as defined above, in which R''_3 contains a COOH radical, is carried out under standard conditions. A primary or secondary amine can be used on a functional derivative of the acid for example a symmetrical or mixed anhydride.

Also a subject of the present invention is a preparation process for products of formula (I'):

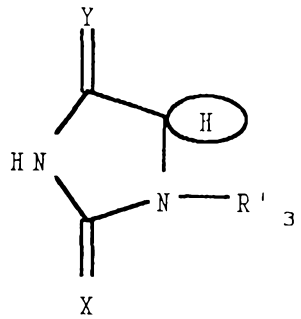


(I')

in which Ar, X, Y, R'_3 and (H) have the meanings indicated above, characterized in that a product of formula (VIII):

Ar-Hal (VIII)

in which Ar has the previous meaning and Hal represents a halogen atom, is reacted with a product of formula (IX):



(IX)

in which X, Y, R'_3 and (H) have the meanings indicated above, the reaction being carried out in the presence of a catalyst and optionally of a solvent.

As far as the products of formula (VIII) are concerned,

the term Hal preferably designates the chlorine atom, but can also represent a bromine or iodine atom.

The role of the catalyst is probably to trap the hydrogen halide which is released and thus to facilitate the condensation reaction of the product of formula (VIII) with the product of formula (IX) to give the desired product.

A more particular subject of the invention is a process as defined above in which the catalyst is a metal in native or oxidized form or a base.

When the catalyst used is a metal, this metal can be copper or nickel. It can be in native form, in the form of metallic oxide or also in the form of metallic salts.

The metallic salts can be a chloride or an acetate.

When the catalyst is a base, this base can be for example soda or potash and if desired, dimethylsulphoxide can be added to the reaction medium.

A more particular subject of the invention is a process as defined above in which the catalyst is chosen from cuprous oxide, cupric oxide, copper in native form and a base such as soda or potash.

The copper in native form used as catalyst is preferably in the form of a powder.

A particular subject of the invention is a process as defined above in which the catalyst is cuprous oxide.

The solvent used is preferably chosen from ethers with a high boiling point such as, for example, phenyl oxide, diglyme, triglyme and dimethylsulphoxide but can also be, for example, an oil with a high boiling point such as paraffin or vaseline.

A more particular subject of the invention is a process as defined above characterized in that the operation is carried out in the presence of a solvent of ether type such as phenyl oxide, diglyme, triglyme or dimethylsulphoxide.

A quite particular subject of the invention is a process as defined above in which the solvent used is phenyl oxide or triglyme.

The preparation process for the desired product defined above can be carried out under pressure or at atmospheric

pressure, preferably at a high temperature.

Therefore a subject of the invention is a process as defined above characterized in that the reaction is carried out at a temperature greater than 100°C and preferably greater than 150°C.

A more particular subject of the invention is a process as defined above characterized in that the reaction is carried out for more than 2 hours.

A very particular subject of the invention is a process as defined above characterized in that the reaction is carried out in the presence of cuprous oxide, in triglyme, at a temperature greater than or equal to 200°C and for more than 3 hours.

The products which are a subject of the present invention possess useful pharmacological properties, in particular they fix on the androgen receptor and they have an anti-androgen activity.

Tests given in the experimental part illustrate these properties.

These properties make the products of formula (I) as defined above of the present invention usable as medicaments mainly for:

- the treatment of adenomas and neoplasias of the prostate as well as benign hypertrophy of the prostate, on their own or in combination with analogues of LHRH. They can also be used in the treatment of benign or malignant tumours possessing androgen receptors and more particularly cancers of the breast, the skin, the ovaries, the bladder, the lymphatic system, the kidney and the liver,
- the treatment of cutaneous diseases such as acne, hyperseborrhoea, alopecia or hirsutism. These products can therefore be used in dermatology on their own or in combination with antibiotics such as the derivatives of azelaic and fusidic acids, erythromycin, as well as derivatives of retinoic acid or an inhibitor of 5 -reductase such as (5α,17β)-1,1-dimethylethyl 3-oxo 4-aza-androst-1-ene 17-carboxamide (or Finasteride, Merck 11th ed.) for the treatment of acne, alopecia or hirsutism. They can also be

combined with a product stimulating hair growth such as Minoxidil for the treatment of alopecia.

The products of formula (I) as defined above can also be used in the veterinary domain for the treatment of behavioural disorders such as agressiveness, androgen-dependent disease, such as circum analum in dogs and tumours having androgen receptors. They can also be used to cause a chemical castration in animals.

The products of formula (I), as defined above, in radioactive form (tritium, carbon 14, iodine 125 or fluorine 18) can also be used as specific labels for the androgen receptor. They can also be used in diagnostics in medical imagery.

Therefore a subject of the invention is the use, as medicaments, of the pharmaceutically acceptable products of formula (I) as defined above, and particularly of the pharmaceutically acceptable products of formula (F) as defined above.

A more particular subject of the invention is the use, as medicaments, of the following products:

- 4-(2,4-dioxo 1-(4-hydroxybutyl) 8-oxa 1,3-diazaspiro (4.5)decan 3-yl) 2-(trifluoromethyl) benzonitrile,
- 4-(2,4-dioxo 1-(2-fluoroethyl) 8-oxa 1,3-diazaspiro (4.5)decan 3-yl) 2-(trifluoromethyl) benzonitrile,
- 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 8-oxa 1,3-diazaspiro (4.5)decane 1-acetonitrile,
- 4-(2,4-dioxo 1-(4-hydroxybutyl) 8-thia 1,3-diazaspiro (4.5)decan 3-yl) 2-(trifluoromethyl) benzonitrile.

The products can be administered by parenteral, buccal, perlingual, rectal or topical route.

Also a subject of the invention is the pharmaceutical compositions, characterized in that they contain, as active ingredient, at least one of the medicaments as defined above.

These compositions can be presented in the form of solutions or injectable suspensions, tablets, coated tablets, capsules, syrups, suppositories, creams, ointments, gels and lotions. These compositions can also be presented in the form of liposomes. These pharmaceutical forms are prepared

according to the usual methods. The active ingredient can be incorporated with the excipients usually employed in these compositions, such as aqueous or non-aqueous vehicles, talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, fatty substances of animal or vegetable origin, paraffin derivatives, glycols, various wetting, dispersing or emulsifying agents, preservatives.

The usual dose, variable according to the patient being treated and the disease in question can be, for example, from 10 mg to 500 mg per day for man, by oral route.

The products of formula (II) used at the start of the invention can be obtained by the action of phosgene when X represents an oxygen atom or of thiophosgene when X represents a sulphur atom on the corresponding amine of formula (A):

$$Ar\text{-}NH_2 \qquad (A)$$

An example of such a preparation is given in the European Patent EP 0494819. When Ar represents a phenyl radical, a product of this type is also described in the French Patent BF 2,329,276 and amines of formula (A) are described in the European Patent EP 0,002,892 or the French Patent BF 2,142,804.

The products of formula (X) are known or can be prepared from the corresponding cyanhydrin according to the process described in the publications: J. Am. Chem. Soc. (1953), 75, 4841, BEIL I 4 526 or J. Org. Chem. 27 2901 (1962).

The products of formula (X) in which R'_3 is different from a hydrogen atom can be obtained by the action of a product of formula R''_3 Hal on 2-cyano 2-amino propane under the conditions stated above for the action of R''_3 Hal on the products of formula (Ia). An example of a preparation of this type is described in the reference:

- Jilek et al. Collect. Czech. Chem. Comm. 54(8) 2248 (1989).

The products of formulae (VIII) and (IX), used at the start of the process indicated above, for obtaining products of formula (I'), as defined above, are known and commercially

available or can be prepared according to methods known to a man skilled in the art.

The preparation of the products of formula (IX) is described in particular in the following publications:

- Zhur. Preklad. Khim. 28, 969-75 (1955) (CA 50, 4881a, 1956)
- Tetrahedron 43, 1753 (1987)
- J. Org. Chem. 52, 2407 (1987)
- Zh. Org. Khim. 21, 2006 (1985)
- J. Fluor. Chem. 17, 345 (1981)

or in the Patents:

- German DRP 637,318 (1935)
- European EP 0,130,875
- Japanese JP 81,121,524.

The products of formula (IX) which are derivatives of hydantoin are widely used and mentioned in the literature such as for example in the following articles:

- J. Pharm. Pharmacol., 67, Vol. 19(4), p. 209-16 (1967)
- Khim. Farm. Zh., 67, Vol. 1 (5) p. 51-2
- German Patent 2,217,914
- European Patent 0,091,596
- J. Chem. Soc. Perkin. Trans. 1, p. 219-21 (1974).

The products of formula (III) as defined above are commercially available, such as in particular those used in the preparation of the examples described hereafter. There can be mentioned for example:

4-amino-tetrahydro-2H-pyran-4-carbonitrile
4-amino tetrahydro-2H-thiopyran 4-carbonitrile
4-amino 1-methyl piperidine 4-carbonitrile.

Also the subject of the invention is, as a new industrial product and in particular as a new industrial product which can be used as an intermediate for the preparation of the products of formula (I), as defined above, the products of formulae (IV) as defined above in which Ar has the meaning indicated above with the exception of the phenyl radical substituted by two radicals chosen from the halogen atoms and cyano, nitro, trifluoromethyl and free, salified, amidified or esterified carboxy radicals.

The following examples illustrate the invention without

however limiting it.

EXAMPLE 1: 4-(4-imino 2-oxo 8-oxa 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

STAGE 1: 4-amino-tetrahydro-2H-pyran-4-carbonitrile

8 ml of ammonium hydroxide, 1.58 g of ammonium chloride and 1.23 g of sodium cyanide are successively introduced, the solution obtained is cooled down in an ice/methanol bath at about -7°C and 2 ml of tetrahydro-4H-pyran 4-one is added at a temperature of ≤ 0°C, the reaction medium is left to rise to ambient temperature and agitated vigorously for 18 hours. After extracting 3 times with methylene chloride, washing with salt water and drying, 2.49 g of expected product (translucent crystals) is obtained. M.p. = approx. 46-47°C.

Physical analyses:

I.R.: ($CHCl_3$) cm^{-1}

NH_2	3390-3374-3324
C≡N	2225
NH_2 def.	1605

STAGE 2: 4-(4-imino 2-oxo 8-oxa 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

883 mg of the product obtained in Stage 1 above is introduced into 7 ml of 1,2-dichloroethane and 0.3 ml of triethylamine.

6.4 ml of the product obtained in the preparation of Example 7 of the European Patent Application EP 0494819 is brought to about -7°C and added dropwise over 15 minutes, then the whole is left to return to ambient temperature.

The reaction medium is left for one hour, evaporated to dryness and purified on silica with methylene chloride - acetone: 7/1 as eluant. In this way 1.85 g of expected product (white crystals) is obtained, M.p. = 249-250°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

OH/NH	3340-3295
C≡N	2240
C=O	1750
Conjugated system aromatic	1678-1612-1572-1508

EXAMPLE 2: 4-(2,4-dioxo 8-oxa 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

1.66 g of the product of Example 1 is introduced into 30 ml of methanol, 10 ml of chloroform, 10 ml of 2N hydrochloric acid, and the mixture is taken to reflux for 50 minutes, 100 ml of water is added and extraction is carried out 3 times with ethyl acetate. The organic phase is washed with salt water, dried and purified on silica with methylene chloride - acetone: 85-15 as eluant. The resultant product is dissolved in 100 ml of isopropanol at about 70°C, filtration is carried out, followed by concentrating, ice-cooling for one hour, separating and drying. In this way 1.425 g of expected product (white crystals) is obtained. M.p. = 192-193°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

Adsorption OH/NH	
C≡N	2240
C=O	1790-1732
Aromatics	1614-1582-1506

EXAMPLE 3: 4-(2,4-dioxo 1-(4-hydroxybutyl) 8-oxa 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

55 mg of 50% sodium hydride is introduced, 340 mg of the product of Example 2 and 25 ml of dimethylsulphoxide are added dropwise over 25 minutes. Rinsing is carried out with 0.5 ml of dimethylsulphoxide and 20 minutes after the release of hydrogen has stopped, 0.41 g of 4-iodobutoxy trimethylsilane is added, and the whole is left to react for 18 hours at ambient temperature.

The reaction medium is then poured into 10 ml of water and extraction is carried out 4 times with ether. The organic phase is washed with water then with salt water, dried and taken up in a mixture of 10 ml of methanol and 1 ml of 2N hydrochloric acid. After 30 minutes, the mixture is poured into 20 ml of saturated sodium chloride solution and extraction is carried out 3 times with chloroform, followed by drying. Purification is carried out on silica with methylene chloride - acetone 8-2 as eluant and 369 mg of expected product (friable white foam) is obtained.

Physical analyses:

I.R.: ($CHCl_3$) cm^{-1}

OH	3626-3485
C≡N	2235
C=O	1775-1721
Aromatics	1615-1602-1577-1505

EXAMPLE 4: 4-(2,4-dioxo 1-(2-hydroxyethyl) 8-oxa 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

82 mg of 50% sodium hydride, 510 mg of the product of Example 2, 4 ml of dimethylsulphoxide are mixed together, rinsed with 0.5 ml of dimethylsulphoxide and 20 minutes after the release of hydrogen has stopped, 572 mg of 2-iodoethoxy dimethylterbutyl silane is added in one go and the solution is taken to 40°C for one hour 30 minutes then to ambient temperature for 18 hours. The reaction medium is poured into 40 ml of water containing 0.2 g of monopotassium phosphate and extraction is carried out 4 times with ether, the extracts are washed with water then with salt water and dried. Purification is carried out on silica with methylene chloride - ethyl acetate as eluant. The residue is taken up in 16 ml of methanol, 3 ml of 2N hydrochloric acid and heating to 40°C is carried out for 40 minutes. The resultant mixture is poured into 50 ml of 50% sodium bicarbonate, extraction is carried out 3 times with chloroform, the extracts are washed with salt water and dried. Purification on silica is carried out with methylene chloride - acetone: 8-2 as eluant and 451 mg of expected product (white crystals) is obtained. M.p. = 196-197°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

OH/NH	3450
C≡N	2240
>=O	1775-1718
Aromatics	1615-1576-1508

EXAMPLE 5: 4-(2,4-dioxo 1-(3-hydroxypropyl) 8-oxa 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

The operation is proceeded with as in Example 4, starting with 109 mg of 50% sodium hydride, 510 mg of the

product of Example 2 and 4 ml of dimethylsulphoxide and rinsing is carried out with 0.5 ml of dimethylsulphoxide then 20 minutes after the release of hydrogen has stopped, 1.004 g of 3-bromopropoxydiphenyl tert-butyl silane is added and the solution is taken to about 50°C. Proceeding as in Example 4, the solution is taken up in 30 ml of methanol, 10 ml of 2N hydrochloric acid, 10 ml of chloroform and taken to reflux.

After purification on silica with methylene chloride - acetone: 8-2 as eluant, 441 mg of expected product (white crystals) is obtained. M.p. = 155-156°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

General adsorption NH/OH	
C≡N	2240
>=O	1778-1714
Aromatics	1618-1580-1539-1511

EXAMPLE 6: Ethyl 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 8-oxa 1,3-diazaspiro[4.5]decane 1-butanoate

The operation is carried out as in Example 3 starting with 123 mg of 50% sodium hydride, 510 mg of the product of Example 2, 3.5 ml of dimethylsulphoxide, rinsing with 0.5 ml of dimethylsulphoxide, and 15 minutes after the release of hydrogen has stopped, 454 mg of ethyl 4-bromobutyrate is added and the solution is taken to 40°C for 50 minutes. It is poured into 40 ml of water containing 0.4 g of monopotassium phosphate, extraction is carried out 4 times with ether, the organic phase is washed with water then with salt water, dried and purified on silica with methylene chloride - ethyl acetate: 85-15 as eluant. In this way 584 mg of expected product (white crystals) is obtained. M.p. = 129-130°C.

Physical analyses:

I.R.: ($CHCl_3$) cm^{-1}

C≡N	2230
>=O	1776-1722
Aromatics	1614-1575-1505

EXAMPLE 7: 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 8-oxa 1,3-diazaspiro[4.5]decane 1-butanoic acid

522 mg of the product of Example 6 and 20 ml of methanol are mixed together, the solution is heated to 30°C, returned to ambient temperature then 2 ml of 2N soda is added and the reaction medium is left for 4 hours 30 minutes then poured into 30 ml of H_2O and adjusted to pH 2-3. Extraction is carried out 3 times with ethyl acetate, the organic phase is washed with water then with salt water, dried and purified on silica with methylene chloride - methanol: 9-1 as eluant, then solidification is carried out by trituration in 0.2 ml of isopropanol, 5 ml ether. In this way 345 mg of expected product (white crystals) is obtained. M.p. = 151-152°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

Complex adsorption	NH/OH
C≡N	2240
>=O	1780-1720
Aromatics	1615-1581-1510

EXAMPLE 8: 3-(4-methoxyphenyl) 8-oxa 1,3-diazaspiro[4.5]-decane 2,4-dione

The operation is carried out as in Stage 2 of Example 1 starting with 380 mg of the product obtained in Stage 1 of Example 1, 4 ml of 1,2-dichloroethane and 0.25 ml of triethylamine and bringing to -5°C then adding dropwise 450 mg of 4-methoxyphenyl isocyanate, followed by rinsing with 1 ml of 1,2-dichloroethane and leaving the reaction medium to rise to ambient temperature. After one hour, separation is carried out, followed by drying then taking up in 20 ml of methanol, 6 ml of chloroform, 6 ml of 2N hydrochloric acid and taking the solution obtained to reflux for 2 hours. The solution is concentrated, the concentrate is taken up in 30 ml of water, extraction is carried out 5 times with ethyl acetate, the organic phase is washed with 50% sodium bicarbonate, then with salt water, dried and purified on silica with methylene chloride - acetone: 85-15 as eluant. 493 mg of expected product (white crystals) is obtained.

M.p. = 253-254°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

Adsorption region OH/NH

C=O	1774-1715
Aromatics	1609-1590-1518.

EXAMPLE 9: 4-(2,4-dioxo 1-(2-fluoroethyl) 8-oxa 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

55 mg of 50% sodium hydride is introduced, 340 mg of the product of Example 2 and 3 ml of dimethylsulphoxide are added dropwise over about 20 minutes and the solution is rinsed with 0.2 ml of dimethylsulphoxide. 20 minutes after the release of hydrogen has stopped, 0.1 ml of 1-bromo 2-fluoroethane is added and the whole is heated at 50°C for one hour 20 minutes. The reaction medium is poured into 10 ml of ice-cooled water containing 0.2 g of monopotassium phosphate and extraction is carried out 5 times with ether. The organic phase is washed with water then with salt water and dried. The residue is purified on silica with methylene chloride - acetone: 85-15 as eluant, followed by drying and crystallizing from isopropanol. In this way 281 mg of expected product (white crystals) is obtained. M.p. = 192-193°C.

Physical analyses:

I.R.: ($CHCl_3$) cm^{-1}

C=O	1777-1723
C≡N	2238
Aromatics	1616-1576-1505

EXAMPLE 10: 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 8-oxa 1,3-diazaspiro[4.5]decan 1-acetonitrile

55 mg of 50% sodium hydride is introduced and 340 mg of the product of Example 2, 2.5 ml of dimethylsulphoxide are added dropwise over 20 minutes and the reaction medium is rinsed with 0.5 ml of dimethylsulphoxide. 15 minutes after the release of hydrogen has stopped, 0.1 ml of bromoacetonitrile is added and the reaction medium is left for one hour. It is poured into 15 ml of water containing about 0.3 g of monopotassium phosphate, extraction is carried out 3 times with ethyl acetate, the extracts are washed with water then with salt water, dried and purified on silica with methylene chloride - acetone 85-15 as eluant. The resin

obtained is dissolved in a mixture of 15 ml of methylene chloride and 30 ml of isopropanol at about 40°C and concentration is carried out until crystallization is obtained. In this way 267 mg of expected product (white crystals) is obtained. M.p. = 210-211°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

C≡N	2238
>=O	1782-1730
Aromatics	1612-1570-1504

EXAMPLE 11: 3-(4-methylthiophenyl) 8-oxa 1,3-diazaspiro[4.5]-decane 2,4-dione

The operation is carried out as in Example 8, starting with 380 mg of 4-methylthiophenylisocyanate, 4 ml of 1,2-dichloroethane and 0.15 ml of triethylamine.

In this way 513 mg of expected product is obtained.

M.p. = 256 - 257°C.

I.R.: (nujol) cm^{-1}

Adsorption region OH/NH

>=O	1776-1720
Aromatics	1500

EXAMPLE 12: 4-(4-imino 2-oxo 8-thia 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

STAGE 1 4-amino tetrahydro-2H-thiopyran 4-carbonitrile

The operation is carried out as in Stage 1 of Example 1 starting with 8 ml of ammonium hydroxide, 1.58 g of ammonium chloride, 1.23 g of sodium cyanide, 2.51 g of tetrahydro 4H-thiopyran 4-one and the whole is agitated for 18 hours at ambient temperature. Extraction is carried out 3 times with methylene chloride, followed by washing with salt water and drying. In this way 2.88 g of expected product (white crystals) is obtained. M.p. = 51-52°C.

Physical analyses:

I.R.: ($CHCl_3$) cm^{-1}

NH_2	3398-3381-3321
NH_2 def	1617-1584
C≡N	2225

STAGE 2: 4-(4-imino 2-oxo 8-thia 1,3-diazaspiro[4.5]decan 3-

yl) 2-(trifluoromethyl) benzonitrile

The operation is carried out as in Stage 2 of Example 1, starting with 1.42 g of the product obtained in Stage 1 above, 14 ml of 1,2-dichloroethane, 0.5 ml of triethylamine, the reaction medium is taken to a temperature comprised between -10°C and -5°C over about 20 minutes and 9.1 ml of the product obtained in the preparation of Example 7 of the European Patent Application EP 0494819 is added and the whole is left to return to ambient temperature. The reaction medium is left for one hour 20 minutes, followed by drying and purifying on silica with methylene chloride - acetone: 9-1 as eluant, and in this way 2.49 g of expected product (white crystals) is obtained. M.p. = 226-227°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

NH	3330-3250-3210-3170-3120
C≡N	2240
C=O	1750
C=N	1675-1658
Aromatics	1612-1572-1510.

EXAMPLE 13: 4-(2,4-dioxo 8-thia 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

The operation is carried out as in Example 2, starting with 2.34 g of the product of Example 12, 25 ml of methanol, 5 ml of chloroform, 4.5 ml of 2N hydrochloric acid is added and the reaction medium is taken to reflux for one hour. After purification on silica with methylene chloride - acetone: 95-5 as eluant, recrystallization from isopropanol is carried out. In this way 368 mg of expected product (white crystals) is obtained. M.p. = 209-210°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

OH/NH	3340
C≡N	2245
>C=O	1781-1736
Aromatics	1612-1576-1508.

EXAMPLE 14: 4-(2,4-dioxo 1-(4-hydroxybutyl) 8-thia 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

The operation is carried out as in Example 3 starting with 55 mg of 50% sodium hydride, 355 mg of the product of Example 13, 2.5 ml of dimethylsulphoxide are added dropwise over 20 minutes and rinsing is carried out with 0.5 ml of dimethylsulphoxide. 20 minutes after the release of hydrogen has stopped, 0.41 g of 4-iodo butoxy trimethylsilane is added. The reaction medium is then poured into 25 ml of water containing 0.1 g of monopotassium phosphate, extraction is carried out 3 times with ether, the organic phase is washed with water then with salt water and dried. The resultant product is taken up in 10 ml of methanol, 1 ml of 2N hydrochloric acid, left for 30 minutes, poured into 30 ml of 50% sodium chloride and extraction is carried out 3 times with ethyl acetate, then the extracts are washed with salt water and dried. Purification is carried out on silica with methylene chloride - acetone: 9-1 as eluant and in this way 317 mg of expected product (white crystals) is obtained.

M.p. = 139-140°C.

Physical analyses:

I.R.: ($CHCl_3$) cm^{-1}

OH	3628
C≡N	2235
>C=O	1774-1722
Aromatics	1615-1601-1505.

EXAMPLE 15: 4-(2,4-dioxo 8,8-dioxido 8-thia 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

355 mg of the product of Example 12 and 4 ml of methylene chloride are mixed together and 990 mg of metachloroperbenzoic acid, 20 ml of methylene chloride are added over 20 minutes between 22 and 25°C, and the solution is rinsed with 1 ml of methylene chloride. It is left for one hour, 15 ml of sodium thiosulphate is added and vigorous agitation is carried out for 10 minutes. 15 ml of a saturated solution of sodium bicarbonate is added, followed by extracting 3 times with ethyl acetate, washing with water then with salt water and drying. The residue is purified on silica with methylene chloride - acetone: (95-5) as eluant followed by crystallizing from isopropanol. In this way 365

mg of expected product (white crystals) is obtained.
M.p. = 257-258°C.
Physical analyses:
I.R.: (nujol) cm^{-1}

C≡N	2235
>=O	1790-1735
SO_2	1297-1133
Aromatics	1613-1575-1508.

EXAMPLE 16: 4-(2,4-dioxo 8-oxido 8-thia 1,3-diazaspiro[4.5]-decan 3-yl) 2-(trifluoromethyl) benzonitrile (isomer "A")

355 mg of the product of Example 13, 20 ml of methanol, 4 ml of aqueous solution of sodium metaperiodate are mixed together and taken to reflux. The methanol is evaporated off, the residue is taken up in 20 ml of water and extraction is carried out 4 times with ethyl acetate, the organic phase is washed with salt water and dried. Purification is carried out on silica with methylene chloride - methanol: 95-5 as eluant and 900 mg of isomer "A" sulphoxide is collected. It is recrystallized from acetone and 292 mg of expected product called isomer "A" is obtained. M.p. = 260-277°C.
Physical analyses:
I.R.: (nujol) cm^{-1}

General adsorption NH/OH	
C≡N	2235
>=O	1789-1725
S-->O	1010
Aromatics	1612-1572-1509.

EXAMPLE 17: 4-(2,4-dioxo 8-oxido 8-thia 1,3-diazaspiro[4.5]-decan 3-yl) 2-(trifluoromethyl) benzonitrile (isomer "B")

The operation is carried out as in Example 16 and purification is carried out on silica with methylene chloride - methanol 9-1 as eluant.

80 mg of isomer "B" sulphoxide is obtained which is recrystallized from acetone and in this way 72 mg of expected product called isomer "B" is obtained. M.p. = 295°C.
Physical analyses:
I.R.: (nujol) cm^{-1}
Adsorption NH/OH

C≡N	2240
>C=O	1797-1730
S-->O	1015
Aromatics	1618-1580-1509.

EXAMPLE 18: Ethyl 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 8-thia 1,3-diazaspiro[4.5]decane 1-butanoate

The operation is carried out as in Example 6, starting with 96 mg of 50% sodium hydride, and 390 mg of the product of Example 13, 2.5 ml of dimethylsulphoxide are introduced over about 20 minutes, and the solution is rinsed with 0.5 ml of dimethylsulphoxide. 20 minutes after the release of hydrogen has stopped, 370 mg of ethyl 4-bromobutyrate is added and the solution is taken to 40°C for one hour. It is then poured into 15 ml of ice-cooled water containing 0.1 g of monopotassium phosphate and extraction is carried out 4 times with ether, the organic phase is washed with water then with salt water and dried. After purification on silica with methylene chloride - ethyl acetate: 95-5 as eluant, 449 mg of expected product (friable white foam) is obtained.

Physical analyses:

I.R.: ($CHCl_3$) cm^{-1}

C≡N	2236
>=O	1774-1723
Aromatics	1615-1575-1505.

EXAMPLE 19: 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 8-thia 1,3-diazaspiro[4.5]decane 1-butanoic acid

The operation is carried out as in Example 7 starting with 440 mg of the product of Example 18, 20 ml of methanol, 2 ml of 2N soda, agitation is carried out for 3 hours 30 minutes at ambient temperature and 3 ml of 2N hydrochloric acid is added. Purification is carried out on silica with methylene chloride - methanol: 95-5 as eluant and 346 mg of expected product (white crystals) is obtained. M.p. = 197-198°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

C≡N	2235
>=O	1770-1725

Acid	1710
Aromatics	1615-1575-1505.

EXAMPLE 20: 4-(4-imino 8-methyl 2-thioxo 1,3,8-triazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

STAGE 1: 4-amino 1-methyl piperidine 4-carbonitrile

The operation is carried out as in Stage 1 of Example 1, starting with 8 ml of ammonium hydroxide, 1.58 g of ammonium chloride, 1.23 g of sodium cyanide and 2.5 ml of 1-methylpiperidone is added. Agitation is carried out for 18 hours at ambient temperature, followed by extraction 3 times with chloroform, the organic phase is washed with salt water and dried. In this way 2.41 g of expected product (orange-yellow syrup) is obtained.

Physical analyses:

I.R.: ($CHCl_3$) cm^{-1}

NH_2	3378-3320
C≡N	2226
NH_2 def.	1602

STAGE 2: 4-(4-imino 8-methyl 2-thioxo 1,3,8-triazaspiro[4.5]-decan 3-yl) 2-(trifluoromethyl) benzonitrile

The operation is carried out as in Stage 2 of Example 1, starting with 140 mg of the product obtained in Stage 1 above, 1.5 ml of 1,2-dichloroethane, 0.1 ml of triethylamine and 230 mg of the product obtained in the preparation of Example 11 of the European Patent Application EP 0494819 and 1.5 ml of 1,2-dichloroethane are added dropwise. The reaction medium is left for 2 hours, evaporated to dryness and the residue is purified on silica with methylene chloride - acetone: 8-2 as eluant. In this way 315 mg of expected product (ivory crystals) is obtained. M.p. > 264°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

NH	3190
C≡N	2240
>=NH	1700-1688-1678
Aromatics	1618-1580-1518-1505

EXAMPLE 21: 4-(8-methyl 4-oxo 2-thioxo 1,3,8-triazaspiro-[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

300 mg of the product of Example 20, 6 ml of methanol, 1.5 ml of 2N hydrochloric acid are mixed together and taken to reflux for one hour then returned to ambient temperature, the reaction medium is poured into 20 ml of 50% ammonium hydroxide, saturated with sodium chloride, extraction is carried out 3 times with ethyl acetate and the extracts are dried. Purification is carried out on silica with methylene chloride - methanol: 9-1 as eluant. In this way 260 mg of expected product (white crystals) is obtained. M.p. = 229-230°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

OH/NH	3330-3340 + associated
C≡N	2236
C=O	1757
Aromatics	1614-1580-1514-1502

EXAMPLE 22: 4-(4-imino 8-methyl 2-oxo 1,3,8-triazaspiro-[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

The operation is carried out as in Stage 2 of Example 20, starting with 153 mg of the product obtained in Stage 1 of Example 20, 1.5 ml of 1,2-dichloroethane and 0.1 ml of triethylamine, the solution is placed in an ice-cooled water bath, 1 ml of the product obtained in the preparation of Example 7 of the European Patent Application EP 0494819 is added and the whole is left to return to ambient temperature. The reaction medium is left for one hour, dried and the residue is purified on silica with methylene chloride - methanol: 7-3 as eluant. In this way 277 mg of expected product (white crystals) is obtained. M.p. = 199-200°C.

Physical analyses:

I.R.: (nujol) cm^{-1}

NH	3290-3240-3130
C≡N	2224
C=O	1746
C=NH	1677-1669
Aromatics	1609-1568-1512.

EXAMPLE 23: 4-(2,4-dioxo 8-methyl 1,3,8-triazaspiro[4.5]-decan 3-yl) 2-(trifluoromethyl) benzonitrile

The operation is carried out as in Example 2 starting with 3 g of the product of Example 22, 70 ml of methanol, 17 ml of 2N hydrochloric acid and the solution is taken to reflux for one hour 30 minutes. It is poured into 200 ml of ammonium hydroxide + 100 g of ice saturated with sodium chloride, extraction is carried out 4 times with ethyl acetate, the extracts are washed with salt water, dried and purified on silica with methylene chloride - methanol: 9-1 as eluant. After crystallization from methylene chloride - isopropyl ether, 2.12 g of expected product (white crystals) is obtained. M.p. = 188-189°C.

Physical analyses:

I.R.: ($CHCl_3$) cm^{-1}

=C-NH	3445
C≡N	2230
>=O	1789-1729
Aromatics	1615-1576-1505.

EXAMPLE 24: 4-(8,8-dimethyl) 2,4-dioxo 7,9-dioxa 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

STAGE 1: 1,3 bis [(tetrahydro 2H pyran-2-yl)oxy] 2-propanone

9 g of 2,5-dihydroxy 1,4-dioxane 2,5-dimethanol is introduced into 60 ml of dioxane and the suspension is taken to about 70°C for 15 minutes then taken to ambient temperature. Then 20 ml of 3,4-dihydro 2H-pyran and 300 mg of monohydrated paratoluene sulphonic acid are added the temperature is maintained at about 40°C then the reaction medium is left overnight at ambient temperature.

It is then poured into a mixture of 300 ml of a saturated solution of sodium bicarbonate + 10 ml of triethylamine and extraction is carried out 4 times with methylene chloride. The organic phase is washed with salt water and dried.

After purification by passing through silica with ethyl cycloacetate/triethylamine: 8/2 as eluant, 17 g of expected product (pale yellow syrup) is obtained.

ANALYSES:

IR $CHCl_3$ (cm^{-1})

Absence OH

O=C 1736

STAGE 2: 2-amino 3-((tetrahydro-2H-pyran-2-yl) oxy) 2-(((tetrahydro-2H-pyran-2-yl) oxy) methyl) propanenitrile

5.6 g of the product obtained in Stage 1 above is introduced into 8 ml of ammonium hydroxide, the mixture is brought to about -5°C and 1.58 g of ammonium chloride and 1.23 g of sodium cyanide are added successively and the whole is left to return to ambient temperature for about 40 minutes then heated to 40°C ± 5°C under agitation overnight. The reaction medium is returned to ambient temperature and extraction is carried out 3 times with chloroform, the organic phase is washed with salt water and dried.

After purification on silica with ethyl cycloacetate/triethylamine: 3/7 as eluant, 4.41 g of expected product (pale yellow syrup) is obtained.

ANALYSES:

IR $CHCl_3$ (cm^{-1})

-CN	2235
NH_2	3390-3317

STAGE 3: 4-(5-imino-2-oxo-4,4-bis (((tetrahydro-2H-pyran-2-yl) oxy) methyl) 1-imidazolidinyl) 2-(trifluoromethyl) benzonitrile

570 mg of the product obtained in Stage 2 above is introduced into 5 ml of isopropyl ether and 0.28 ml of triethylamine and the mixture is brought to -30°C then a solution of 1,2-dichloroethane at 18.4 g %g and 2.32 g of the product obtained in preparation 1 are added over one hour.

4 ml of methylene chloride is added then the reaction medium is left to return to ambient temperature, left for about 2 hours and dried. After purification on silica with methylene chloride/acetone 9/1 as eluant, 700 mg of expected product is obtained.

ANALYSES:

IR $CHCl_3$ (cm^{-1})

NH	3442-3317
-CN	2235
C=O	1757
C=N	1670

Aromatic 1614-1575-1505

STAGE 4: 4-(4,4-bis(hydroxymethyl)-2,5-dioxo-1-imidazolidinyl)-2-(trifluoromethyl)-benzonitrile

300 mg of the product obtained in Stage 3 above is introduced into 3 ml of methanol and 1.5 ml of 2N hydrochloric acid and the mixture is taken to reflux for one hour 30 minutes.

It is returned to ambient temperature, poured into 5 ml of bicarbonate, extraction is carried out 4 times with ethyl acetate then the extracts are washed with a saturated solution of sodium chloride and dried.

Purification is carried out on silica with methylene chloride - methanol: 9/1 as eluant.

The resultant product is taken up in 20 ml of isopropanol under reflux then concentrated and 225 mg of expected product (white crystals) is obtained, M.p.: 207-208°C.

ANALYSES:

IR NUJOL (cm^{-1})

OH/NH	3525-3365-3250
CN	2240
C=O	1778-1738
Aromatic	1618-1578-1506

STAGE 5: 4-(8,8-dimethyl) 2,4-dioxo 7,9-dioxa 1,3-diazaspiro[4.5]decan 3-yl) 2-(trifluoromethyl) benzonitrile

0.329 g of the product obtained in Stage 4 above, 0.5 ml of 2,2-dimethoxypropane, 0.02 g of paratoluene sulphonic acid and 5 ml of acetone are mixed together and left under agitation for 4 hours then the mixture is hydrolyzed with a solution of sodium bicarbonate and extraction is carried out with ethyl acetate. The organic phases are collected, washed with water, dried, filtered and concentrated. Chromatography on silica is carried out with methylene chloride - acetone: 95-5 as eluant.

After recrystallization from isopropanol, 0.240 g of expected product (white crystals) is obtained M.p. = 203°C.

ANALYSES:

IR NUJOL (cm^{-1})

CN	2240
C=O	1782-1730
Aromatics	1615-1580-1507

EXAMPLE 25:

Tablets were prepared having the following composition:

- Product of Example 3 ..... 100 mg
- Excipient s.q. for a tablet made up to ..... 300 mg

(Detail of the excipient: lactose, starch, talc, magnesium stearate).

PHARMACOLOGICAL STUDY OF THE PRODUCTS OF THE INVENTION

Study of the affinity of the products of the invention for the androgen receptor

Male Sprague Dawley EOPS rats weighing 180-200 g, castrated 24 hours previously, are sacrificed, the prostates are removed, weighed and homogenized at 0°C using a Potter glass, in a buffered solution (10mM Tris, 0.25M saccharose, 0.1mM PMSF (phenylmethanesulphonylfluoride), 20mM sodium molybdate, HCl pH 7.4; to which 2mM of DTT (DL dithiothreitol) is added extemporaneously, at a rate of 1 g of tissue per 8 ml of buffer.

The homogenate is then ultracentrifuged at 0°C, for 30 minutes at 209,000 g. Aliquots of the supernatant obtained (=cytosol), are incubated for 30 minutes and for 24 hours at 0°C, with a constant concentration (T) of tritiated testosterone and in the presence of increasing concentrations (0 to 2500.10^{-9}M), either of unlabelled testosterone, or of the products to be tested. The concentration of bound tritiated testosterone (B) is then measured in each incubate by the method of adsorption on carbon dextran.

Calculation of the relative bond affinity (RBA).

The following 2 curves are drawn: the percentage of bound tritiated hormone B/T as a function of the logarithm of the concentration of the unlabelled reference hormone and B/T as a function of the logarithm of the concentration of the unlabelled tested product.

The straight line of the equation $I_{50} = (B/Tmax + B/Tmin)/2$

is determined.

B/T max = % of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T).

B/T min = % of the bound tritiated hormone for an incubation of this tritiated hormone at the concentration (T) in the presence of a large excess of unlabelled hormone (2500.10^{-9}M).

The intersections of the straight line I_{50} and the curves allow the evaluation of the concentrations of the unlabelled reference hormone (CH) and of the tested unlabelled product (CX) which inhibit by 50% the binding of the tritiated hormone on the receptor. The relative bond affinity (RBA) of the tested product is determined by the equation RBA = 100 (CH)/(CX).

The following results are obtained, expressed in RBA.

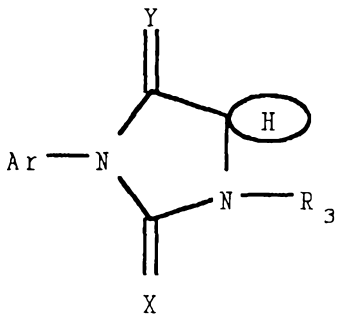
Reference product (Testosterone): 100

Product of Examples	RBA : Incubation 24 hours
3	6
10	5

Where the terms "comprise", "comprises", "comprised" or "comprising" are used in this specification, they are to be interpreted as specifying the presence of the stated features, integers, steps or components referred to, but not to preclude the presence or addition of one or more other feature, integer, step, component or group thereof.

The claims defining the invention are as follows:-

1) Products of formula (I):



(I)

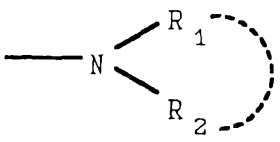
in which (H) represents a saturated heterocyclic radical with 4 to 7 members containing:

either an oxygen, nitrogen or sulphur atom, optionally oxidized, the nitrogen atom being optionally substituted by a radical chosen from the values of R_3,

or two oxygen atoms and optionally one boron atom substituted by a phenyl radical, the heterocycle thus formed being optionally substituted on a carbon atom by an oxo radical, by one or more alkyl radicals, themselves optionally substituted, or by a cycloalkyl radical containing 4 to 7 members,

Ar represents an aryl radical optionally substituted by one or more radicals chosen from:

i) halogen atoms and cyano, nitro, trifluoromethyl, trifluoromethoxy, hydroxyl, free, salified, esterified or amidified carboxy radicals,

ii) the  radical

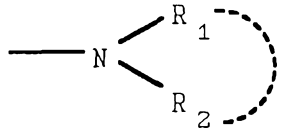
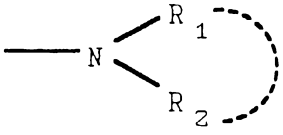
in which the nitrogen atom is optionally oxidized and R_1 and R_2:

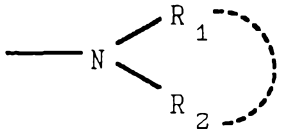
either, identical or different, are chosen from the hydrogen atom and optionally substituted alkyl radicals,

or form together with the nitrogen atom to which they are

linked a monocyclic radical containing 5, 6 or 7 members or a radical constituted by condensed rings containing 8 to 14 members, these identical or different radicals optionally containing one or more other heteroatoms chosen from oxygen, nitrogen and sulphur atoms, and being optionally substituted,

iii) optionally substituted alkyl, alkoxy, alkylthio and arylthio,

iiii) alkyl  and alkoxy 

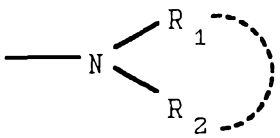
with  as defined above,

X represents an oxygen or sulphur atom,

Y represents an oxygen or sulphur atom or an NH radical

R_3 is chosen from the hydrogen atom, aryl radicals and alkyl, alkenyl and alkynyl radicals optionally interrupted by one or more oxygen, nitrogen or sulphur atoms, optionally oxidized, all these radicals being optionally substituted,

the substituent or substituents of the ring which can be constituted by



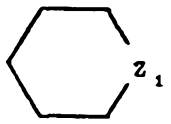
and alkyl, aryl, alkoxy, alkenyl and alkynyl radicals indicated above as optionally substituted, being chosen from halogen atoms and the following radicals: optionally salified, esterified or etherified hydroxy, alkoxy, aryloxy, alkyl, haloalkoxy, haloalkyl, mercapto, alkylthio and

arylthio in which the sulphur atom is optionally oxidized, acyl, acyloxy, free, salified, esterified or amidified carboxy, cyano, nitro, amino, mono or dialkylamino, aryl and arylalkyl, these last two radicals being optionally substituted by one or more radicals chosen from halogen atoms, the following radicals: hydroxyl, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, free, salified or esterified carboxy and tetrazolyl, all the sulphur atoms being optionally oxidized into the sulphoxide or sulphone,

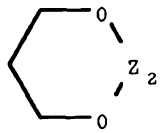
the following products to be excluded:
3-phenyl-8-(phenylmethyl)-1, 3, 8-Triazaspiro(4,5) decan-2, 4-dione;
3-phenyl-8-propyl-1, 3, 8-Triazaspiro(4,5) decan-2, 4-dione;
8-butyl-3-phenyl-1, 3, 8-Triazaspiro(4,5) decan-2, 4-dione;
8-isopropyl-3-phenyl-1, 3, 8-Triazaspiro(4,5) decan-2, 4-dione;
8-butyl-1, 3-diphenyl-1, 3, 8-Triazaspiro(4,5) decan-2, 4-dione;

the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

2) Products of formula (I) as defined in claim 1 in which (H) represents

either the  radical

in which Z_1 represents an oxygen atom, a sulphur atom optionally oxidized in the form of the sulphoxide or sulphone or an $-N-R_4$ radical in which R_4 is chosen from the hydrogen atom and alkyl, alkylphenyl and phenyl radicals optionally substituted by one or more radicals chosen from halogen atoms and hydroxy, alkoxy, free, salified, esterified or amidified carboxy radicals and the phenyl radical itself optionally substituted by one or more radicals chosen from halogen atoms, hydroxyl, alkyl, alkoxy, trifluoromethyl, trifluoromethoxy, nitro, cyano and free, salified or esterified carboxy radicals

or the  radical

in which Z_2 represents either a $-CH_2-$ radical optionally substituted by one or two alkyl radicals, a cycloalkyl radical or an oxo radical containing 4 to 7 members, or a boron atom substituted by a phenyl radical,

Ar represents an aryl radical optionally substituted by one or more radicals chosen from halogen atoms and the following radicals: cyano, nitro, trifluoromethyl, trifluoromethoxy, hydroxyl, free, salified, esterified or amidified carboxy, alkyl, alkoxy, alkylthio, arylthio, amino, mono or dialkylamino, aminoalkyl, mono or dialkylaminoalkyl, aminoalkoxy, mono or dialkylaminoalkoxy, pyrrolidinyl, piperidyl, morpholino and piperazinyl optionally substituted on the second nitrogen atom by an alkyl, phenylalkyl, alkylphenyl or phenyl radical, themselves optionally substituted by one or more radicals chosen from halogen atoms and the hydroxyl and alkoxy radicals,

X represents an oxygen or sulphur atom,

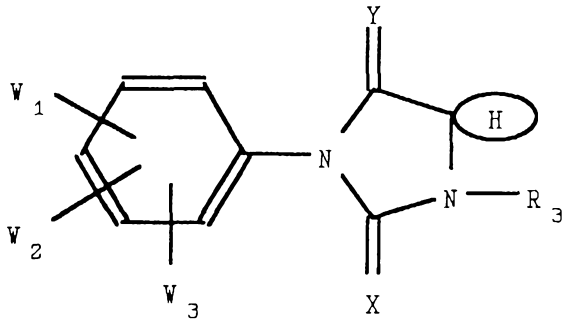
Y represents an oxygen or sulphur atom or an NH radical,

R_3 is chosen from the hydrogen atom, aryl radicals and alkyl, alkenyl and alkynyl radicals optionally interrupted by one or more oxygen, nitrogen or sulphur atoms, optionally oxidized, all these radicals being optionally substituted by one or more radicals chosen from the halogen atoms and the following radicals: optionally salified, esterified or etherified hydroxy, alkoxy, aryloxy, alkyl, trifluoromethyl, trifluoromethoxy, free, salified, esterified or amidified carboxy, cyano, nitro, amino, mono or dialkylamino, phenyl, benzyl and phenethyl themselves optionally substituted by one or more radicals chosen from the halogen atoms and hydroxyl, alkyl, alkoxy, cyano, nitro and trifluoromethyl radicals, the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (I).

3) Products of formula (I) as defined in claim 1 or 2, in which Ar represents a phenyl or pyridyl radical optionally substituted as indicated in claim 2 and (H), R_3, X and Y have

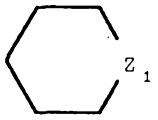
the meanings indicated in claim 1 or 2,
the said products of formula (I) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acid or with mineral and organic bases of the said products of formula (I).

4) Products of formula (I) as defined in any one of claims 1 to 3 and corresponding to formula (F):

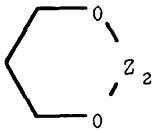


(F)

in which (H) represents:

either the  radical

in which Z_1 represents an oxygen atom, a sulphur atom optionally oxidized in the form of the sulphoxide or sulphone or an $-N-R_4$ in which R_4 is chosen from the hydrogen atom and alkyl radicals, optionally substituted by one or more radicals chosen from halogen atoms and hydroxy, alkoxy and free, salified, esterified or amidified carboxy radicals

or the  radical

in which Z_2 represents either a $-CH_2-$ radical optionally substituted by one or two alkyl radicals, a cycloalkyl radical or an oxo radical containing 4 to 7 members, or a

boron atom substituted by a phenyl radical,
W_1, W_2 and W_3, identical or different, are chosen from the hydrogen atom, halogen atoms and the following radicals: hydroxyl, alkoxy, cyano, amino, mono or dialkylamino, nitro, trifluoromethyl, free, esterified, amidified or salified carboxy, alkylthio and arylthio,
R_3 is chosen from the hydrogen atom and alkyl radicals, optionally substituted by one or more substituents chosen from halogen atoms and optionally salified or etherified hydroxy radicals, alkoxy radicals and free, esterified, amidified or salified carboxy radicals,
X represents an oxygen or sulphur atom,
Y represents an oxygen atom or an NH radical,
the said products of formula (F) being in all the possible racemic, enantiomeric and diastereoisomeric isomer forms, as well as the addition salts with mineral and organic acids or with mineral and organic bases of the said products of formula (F).

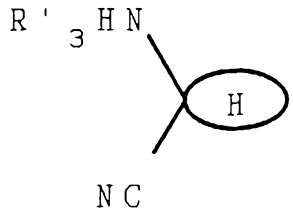
5) The following products:

- 4-(2,4-dioxo 1-(4-hydroxybutyl) 8-oxa 1,3-diazaspiro (4.5)decan 3-yl) 2-(trifluoromethyl) benzonitrile,
- 4-(2,4-dioxo 1-(2-fluoroethyl) 8-oxa 1,3-diazaspiro (4.5)decan 3-yl) 2-(trifluoromethyl) benzonitrile,
- 3-(4-cyano 3-(trifluoromethyl) phenyl) 2,4-dioxo 8-oxa 1,3-diazaspiro(4.5)decane 1-acetonitrile,
- 4-(2,4-dioxo 1-(4-hydroxybutyl) 8-thia 1,3-diazaspiro (4.5)decan 3-yl) 2-(trifluoromethyl) benzonitrile.

6) Preparation process for the products of formula (I) as defined in claim 1, characterized in that a product of formula (II):

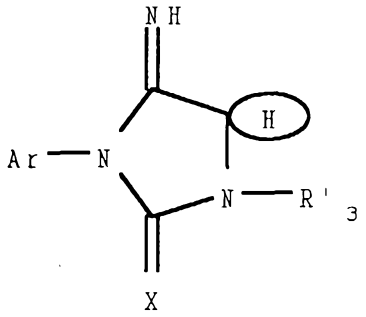
$$Ar-N=C=X \qquad (II)$$

in which X has the meaning indicated in claim 1 and Ar has the meaning indicated in claim 1, in which the optional reactive functions are optionally protected, is reacted, in the presence of a tertiary base,
either with a product of formula (III):



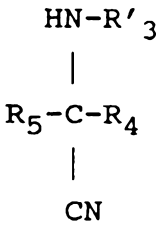
(III)

in which (H) has the meaning indicated in claim 1 and R'_3 has the meaning indicated in claim 1 for R_3 in which the optional reactive functions are optionally protected, in order to obtain a product of formula (Ia):



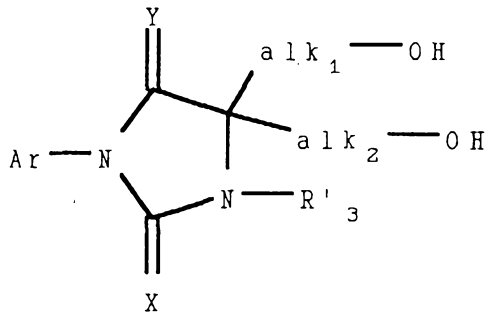
(Ia)

in which Ar, (H) and R'_3 have the meanings indicated above, or with a product of formula (X):



(X)

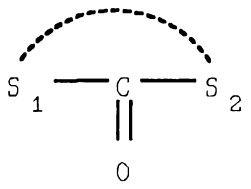
in which R'_3 has the meaning indicated above and R_4 and R_5, identical or different, represent a hydroxyalkyl radical in which the hydroxy function is optionally protected, in order to obtain, if appropriate after deprotection of the hydroxyl radicals, a diol of formula (IV):



(IV)

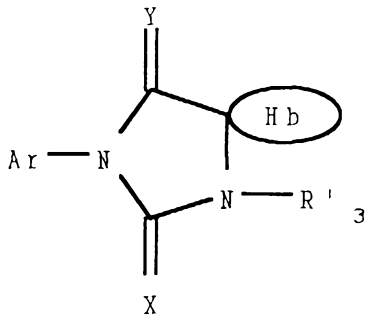
in which Ar, X and R'_3 have the meanings indicated above, Y has the meaning indicated in claim 1 and alk_1 and alk_2, identical or different, represent an alkyl radical, which product of formula (IV) is reacted:

either with a compound of formula (V):



(V)

in which S_1 and S_2, identical or different, represent a hydrogen atom or an alkyl radical, optionally substituted, or S_1 and S_2 form together with C=O a cycloalkanone radical containing 4 to 7 members, in order to obtain a product of formula (Ib):

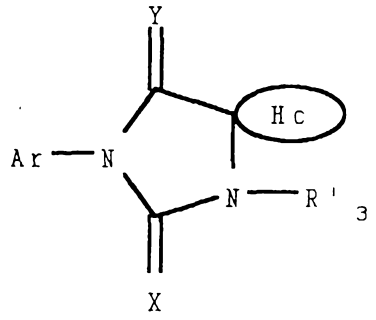


(Ib)

in which (Hb) represents a saturated heterocycle with 4 to 7 members containing two oxygen atoms and optionally substituted by a cycloalkyl radical or by one or two alkyl radicals themselves optionally substituted,

or with phosgene or a derivative of phosgene or N,N'-

carbonyldiimidazole, in order to obtain the product of formula (Ic):



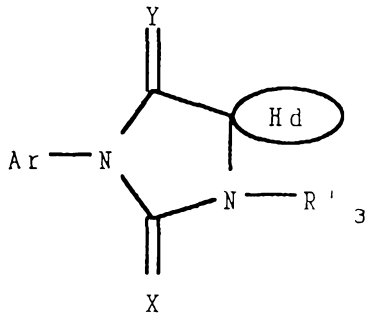
(Ic)

in which Ar, Y, X and R'_3 have the meanings indicated above and (Hc) represents a saturated heterocycle with 4 to 7 members, containing two oxygen atoms and substituted on a carbon atom by an oxo radical,

or with the compound of formula (VI):

$$R\text{-}B(OH)_2 \qquad (VI)$$

in which R represents a phenyl radical, in order to obtain the product of formula (Id):



(Id)

in which Ar, Y, X and R'_3 have the meanings indicated above and (Hd) represents a saturated heterocycle with 4 to 7 members, containing two oxygen atoms and one boron atom substituted by a phenyl radical,

the hydroxyl radicals of which product of formula (IV) can if desired and if necessary be protected in order to obtain a product of formula (IV'),

- which products of formulae (Ia), (Ib), (Ic), (Id) and (IV') thus obtained, as defined above, if appropriate, and if necessary or if desired, can be subjected to any one or more

of the following reactions, in any order:

a) elimination reaction of the optional protective groups which can be carried by R'_3, then if appropriate the action of an esterification, amidification or salification agent,

b) hydrolysis reaction of the >C=NH group into a carbonyl function,

c) conversion of the >C=O group into a >C=S group,

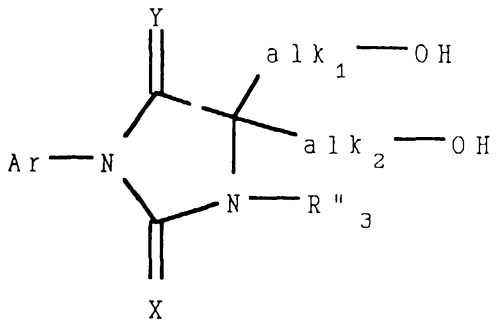
d) conversion of the >C=S group or groups into a >C=O group,

e) when R'_3 represents an alkoxyalkyl radical, conversion reaction of R'_3 into a hydroxyalkyl radical,

f) when R'_3 represents a hydrogen atom, the action of a reagent of formula Hal-R''_3 in which R''_3 has the values of R'_3 with the exception of the hydrogen value and Hal represents a halogen atom, in order to obtain products of formulae (Ia), (Ib), (Ic), (Id) and (IV') as defined above, in which R''_3 has the meaning indicated previously,

g) if desired, the action on the products obtained in f, of an elimination agent of the optional protective groups which can be carried by R''_3 or if appropriate, the action of an esterification, amidification or salification agent,

- which products of formulae (Ib) and (IV') as defined above can be subjected to the reaction indicated above in f) then hydrolyzed into a product of formula (VII):



(VII)

in which Ar, X, Y, alk_1, alk_2 and R''_3 have the meanings indicated above,

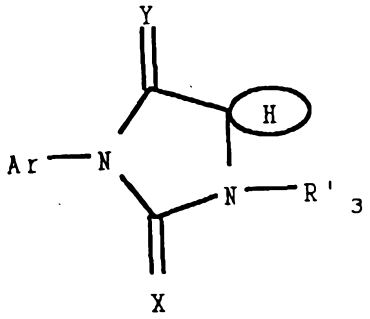
which can be subjected to the same reactions as the product of formula (IV) as defined above, in order to obtain the corresponding products of formula (Ib), (Ic) or (Id) in which R''_3 has the meaning indicated above,

- which products of formulae (Ia), (IV), (IV'), (VII),

(Ib), (Ic) and (Id) as defined above, if appropriate, and if necessary or if desired, can be subjected to any one or more of the following reactions, in any order:

- salification reaction by a mineral or organic acid or by a base in order to obtain the corresponding salt,
- elimination reaction of the optional protective groups which can be carried by the protected reactive functions.

7. Preparation process for the products of formula (I'):

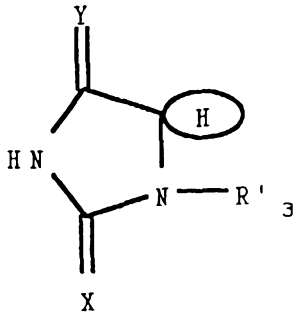


(I')

in which Ar, X, Y, R'_3 and (H) have meanings indicated in claim 1, characterized in that a product of formula (VIII):

(VIII)

in which Ar has the previous meaning and Hal represents a halogen atom, is reacted with a product of formula (IX):



(IX)

in which X, Y, R'_3 and (H) have the meanings indicated in Claim 1.

8. A pharmaceutical composition comprising products of formula (I) as defined in any one of Claims 1 to 3 together with a pharmaceutically acceptable carrier, adjuvant, diluent and/or excipient.

9. A pharmaceutical composition comprising products of formula (F) as defined in Claim 4 together with a pharmaceutically acceptable carrier, adjuvant, diluent and/or excipient.

10. A pharmaceutical composition of Claim 8 or Claim 9, substantially as herein described with reference to any one of the Examples.

11. Products of formula (I) as defined in Claim 1, substantially as herein described with reference to any one of the Examples.

12. Products of formula (F) as defined in Claim 4, subtantially as herein described with reference to any one of the Examples.

13. Preparation process of Claim 6 or Claim 7 which process is substantially as herein described with reference to any one of the Examples.

14. A method for the treatment of adenomas and neoplasias of the prostate as well as benign hypertrophy of the prostate in a patient/mammal requiring such treatment which method comprises administering to said patient/mammal an effective amount of the products of formula (I) as defined in Claim 1 either alone or in combination with analogues of LHRH or an effective amount of pharmaceutical composition as defined in Claim 8.

15. A method for the treatment of benign or malignant tumours possessing androgen receptors and more particularly cancers of the breast, the skin, the ovaries, the bladder, the lymphatic system, the kidney and the liver in a patient/mammal requiring such treatment which method comprises administering to said patient/mammal an effective amount of the products of formula (I) as defined in Claim 1 or a pharmaceutical composition as defined in Claim 8.

16. A method for the treatment of cutaneous diseases in a patient/mammal requiring such treatment which method comprises administering

to said patient/mammal an effective amount of the products of formula (I) as defined in Claim 1 either alone or in combination with antibiotics or a product stimulating hair growth or an effective amount of a pharmaceutical composition as defined in Claim 8.

17. The method as claimed in Claim 16, wherein said cutaneous diseases include acne, hyperseborrhoea, alopecia or hirsutism.

18. The method as claimed in Claim 17, wherein said antibiotics include derivatives of azelaic and fusidic acids, erythromycin, as well as a derivative of retinoic acid or an inhibitor of 5-reductase.

19. The method as claimed in Claim 18, wherein the inhibitor of 5-reductase is (5∝, 17β)-1,1-dimethylethyl 3-oxo 4-aza-androst-1-ene 17-carboxamide.

20. The method as claimed in any one of Claims 16 to 19, wherein the product stimulating hair growth is 6-(1-piperidinyl)-2,4-pyrimidinediamine 3-oxide.

21. A method for the treatment of behavioural disorders, androgen-dependent diseases or tumours having androgen receptors in an animal requiring such treatment which method comprises administering to said animal an effective amount of the products of formula (I) as defined in Claim 1 or a pharmaceutical composition as defined in Claim 8.

22. A method as claimed in Claim 21, wherein said behavioural disorders include aggressiveness.

23. A method as claimed in Claim 21, wherein said androgen-dependent disease is circum analum in dogs.

24. A method of any one of Claims 14 to 23 which method is substantially as herein described.

25. Use of the products of formula (I) as defined in Claim 1 in the preparation of a medicament for the treatment of adenomas and neoplasias of the prostate as well as benign hypertrophy of the prostate.

26. Use of the products of formula (I) as defined in Claim 1 in the

preparation of a medicament for the treatment of benign or malignant tumours possessing androgen receptors and more particularly cancers of the breast, the skin, the ovaries, the bladder, the lymphatic system, the kidney and the liver.

27. Use of the products of formula (I) as defined in Claim 1 in the preparation of a medicament for the treatment of cutaneous diseases.

28. Use of the products of formula (I) as defined in Claim 1 in the preparation of a medicament for the treatment of behavioural disorders, androgen-dependent diseases or tumours having androgen receptors.

29. As a new industrial product and in particular as a new industrial product which can be used as an intermediate for the preparation of the products of formula (I) as defined in Claim 1, the product of formulae (IV) as defined above, in which Ar has the meaning indicated in Claim 1 with the exception of phenyl substituted by two radicals chosen from the halogen atoms and cyano, nitro, trifluoromethyl and free, salified, amidified or esterified carboxy radicals.

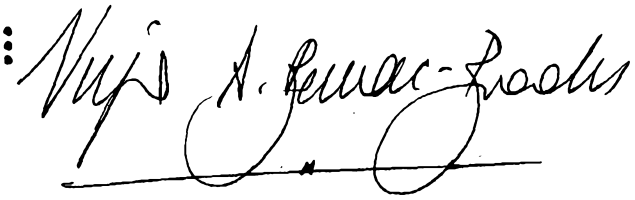
30. Products of claim 5, substantially as herein described with reference to any one of the Examples.

DATED this 9th day of December, 1998.

HOECHST MARION ROUSSEL

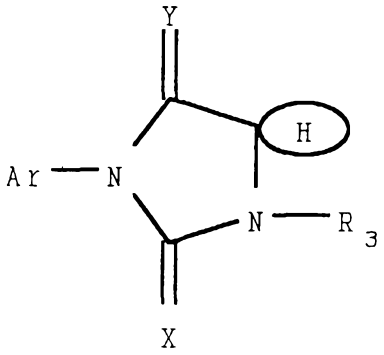
By their Patent Attorneys:

CALLINAN LAWRIE



A B S T R A C T

A particular subject of the invention is the products of formula (I):



(I)

in which:
Ar represents aryl optionally substituted in particular by cyano, nitro, halogen, trifluoromethyl, free, esterified or salified carboxy, alkoxy, alkylthio,
X represents oxygen or sulphur and R_3 represents in particu lar hydrogen, alkyl, alkenyl, alkynyl, aryl or aryl-alkyl, optionally substituted,
Y represents oxygen or sulphur or NH,
(H) represents a saturated heterocycle containing O, S or N, optionally substituted.