COMMONWEALTH OF AUSTRALIA

The Patents Act 1990

PATENT REQUEST: CONVENTION PATENT

We, ROUSSEL UCLAF, being the person identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow:

Applicant: ROUSSEL UCLAF
Address: 35, Boulevard des Invalides, 75007, Paris, France
Nominated Person: ROUSSEL UCLAF
Address: 35, Boulevard des Invalides, 75007, Paris, France
Invention Title: NEW STEROIDS CONTAINING IN POSITION 20 AN AMINOSUBSTITUTED CHAIN, PREPARATION PROCESS AND INTERMEDIATES OF THIS PROCESS, USE AS MEDICAMENTS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

Name of actual Inventors: Armelle Bonfils and Daniel Philibert
Address for service in Australia: CALLINAN LAWRIE, 278 High Street, Kew 3101, Victoria, Australia
Attorney Code: CL

Convention Details

<table>
<thead>
<tr>
<th>Application Number</th>
<th>Country</th>
<th>Country Code</th>
<th>Date of Application</th>
</tr>
</thead>
<tbody>
<tr>
<td>94-03872</td>
<td>France</td>
<td>FR</td>
<td>1 April 1994</td>
</tr>
</tbody>
</table>

DATED this 28th day of March, 1995.

ROUSSEL UCLAF
By their Patent Attorneys: CALLINAN LAWRIE
NOTICE OF ENTITLEMENT

We, ROUSSEL-UCLAF of 35, Boulevard des Invalides, 75007, Paris, France being the applicant and the person nominated for grant of patent in respect of Application for an invention entitled

NEW STEROIDS CONTAINING IN POSITION 20 AN AMINOSUBSTITUTED CHAIN, PREPARATION PROCESS AND INTERMEDIATES OF THIS PROCESS, USE AS MEDICAMENTS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

state the following:-

STANDARD CONVENTION FILING

(a) The person nominated for the grant of the patent:

(i) has entitlement from the actual inventors by virtue of being a person who would, if a patent were to be granted upon an application made by the said inventors, be entitled to have the patent assigned to it; and

(ii) is the applicant of the basic application.

(b) The basic application listed on the request form is the first application made in a Convention country in respect of the invention.

Michael J. Houlihan
Registered Patent Attorney

Date 28 July 1991

To: The Commissioner of Patents
A subject of the invention is the compounds of formula (I):

\[ \text{structure diagram} \]

in which \( R_1 \) and \( R_2 \), identical or different, represent an alkyl having 1 to 12 carbon atoms, an aralkyl having 7 to 15 carbon atoms, or form together with the nitrogen atom to which they are linked a saturated heterocycle with 5 or 6 members optionally containing another heteroatom chosen from oxygen, nitrogen and sulphur, \( R_3 \) in alpha position represents an alkyl having 1 to 8 carbon atoms, \( n \) is comprised between 2 and 15, \( R_4 \) represents an alkyl having 1 to 12 carbon atoms, \( R_5 \) represents a hydrogen, an acyl containing at most 12 carbon atoms or an alkyl containing at most 12 carbon atoms, and the
wavy lines indicate that the asymmetrical centres 17 and 20 can be independent of the absolute R or S configuration, as well as their addition salts, their preparation process, their use as medicaments, the pharmaceutical compositions containing them and the new intermediates obtained.
TO BE COMPLETED BY APPLICANT

Name of Applicant: ROUSSEL UCLAF

Actual Inventors: Armelle Bonfils and Daniel Philibert

Address for Service: CALLINAN LAWRIE, 278 High Street, Kew, 3101, Victoria, Australia

Invention Title: "NEW STEROIDS CONTAINING IN POSITION 20 AN AMINOSUBSTITUTED CHAIN, PREPARATION PROCESS AND INTERMEDIATES OF THIS PROCESS, USE AS MEDICAMENTS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

The following statement is a full description of this invention, including the best method of performing it known to us:-
New steroids containing in position 20 an aminosubstituted chain, preparation process and intermediates of this process, use as medicaments and pharmaceutical compositions containing them.

The present invention relates to new steroids containing in position 20 an aminosubstituted chain, their preparation process and the intermediates of this process, their use as medicaments and the pharmaceutical compositions containing them.

A subject of the invention is the compounds of formula (I):

![Chemical Structure](image)

in which $R_1$ and $R_2$, identical or different, represent an alkyl radical containing 1 to 12 carbon atoms, an aralkyl radical having 7 to 15 carbon atoms, or form together with the nitrogen atom to which they are linked a saturated heterocycle with 5 or 6 members optionally containing another heteroatom chosen from oxygen, nitrogen and sulphur, $R_3$ in alpha position represents an alkyl radical containing 1 to 8 carbon atoms, $n$ designates an integer comprised between 2 and 30, $R_4$ represents an alkyl radical containing 1 to 12 carbon atoms, $R_s$ represents a hydrogen atom, an acyl group containing at most 12 carbon atoms or an alkyl radical containing at most 12 carbon atoms, and the wavy lines indicate that the asymmetrical centres 17 and 20 can be independent of the absolute R or S configuration, as well as their addition salts with acids.

When $R_1$, $R_2$, $R_4$ and $R_s$ represent an alkyl group containing 1 to 12 carbon atoms, it can be one of the
following radicals: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, 2-methyl penty1, 2,3-dimethyl butyl, n-hepty1, 2-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethyl penty1, 3-ethylpentyl, n-octyl, 2,2-dimethylhexyl, 3,3-dimethylhexyl, 3-methyl-3-ethylpentyl, nonyl, 2,4-dimethylheptyl or n-decyl.

It is preferably methyl, ethyl, isopropyl.

When R₁ and R₂ represent an aralkyl group containing 7 to 15 carbon atom, it is preferably a benzyl or phenethyl group.

When R₁ and R₂ form with the nitrogen to which they are linked a saturated heterocycle with 5 or 6 members optionally containing another heteroatom chosen from oxygen, nitrogen and sulphur, it is preferably a piperidino, morpholino, thiomorpholino, piperazino or pyrrolidino group.

When R₃ represents an alkyl group containing 1 to 8 carbon atoms, it can be one of the following radicals: methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, 2-methyl penty1, 2,3-dimethyl butyl, n-hepty1, 2-methylhexyl, 2,2-dimethylpentyl, 3,3-dimethyl pentyl, 3-ethylpentyl. It is preferably methyl.

By acyl group having at most 12 carbon atoms, is preferably meant a group chosen from acetyl, propionyl, butyryl, benzoyl, valeryl, hexanoyl, acryloyl and crotonoyl.

The formyl group can also be mentioned.

The invention naturally extends to the addition salts with acids of the compounds of formula (I), such as for example to the salts formed with the following acids: hydrochloric, hydrobromic, nitric, sulphuric, phosphoric, acetic, formic, propionic, benzoic, maleic, fumaric, succinic, tartaric, citric, oxalic, glyoxylic, aspartic, alkane sulphonic such as methane or ethane sulphonic, ary1sulphonic, such as benzene or paratoluene sulphonic and arylcarboxylic. The addition salts with hydrochloric acid are preferred.

A more particular subject of the invention is the compounds of general formula (I) as defined previously in which n is equal to 2 as well as their addition salts with
acids.

A more particular subject of the invention is the compounds of general formula (I) as defined previously corresponding to general formula (I'):

\[
\text{(I')}
\]

in which \( R_1 \) and \( R_2 \) have the same meaning as previously as well as their addition salts with acids.

A quite particular subject of the invention is the following compounds of formula (I):

20 (20R) (8alpha,9beta,13alpha,14beta,17alpha) 20-(((dimethyl-amino)ethyl)amino) 19-norpregna-1,3,5(10)-trien-3-ol,
(20S) (8alpha,9beta,13alpha,14beta,17alpha) 20-(((dimethyl-amino)ethyl)amino) 19-norpregna-1,3,5(10)-trien-3-ol,
(20R) (8alpha,9beta,13alpha,14beta,17beta) 20-(((dimethyl-amino)ethyl)amino) 19-norpregna-1,3,5(10)-trien-3-ol,
(20S) (8alpha,9beta,13alpha,14beta,17beta) 20-(((dimethyl-amino)ethyl)amino) 19-norpregna-1,3,5(10)-trien-3-ol,
as well as their addition salts with acids.

A quite particular subject of the invention is the following compound of formula (I):

\[
(20S) (8\text{alpha},9\text{beta},13\text{alpha},14\text{beta},17\text{alpha}) 20-(((\text{dimethyl-amino})\text{ethyl})\text{amino}) 19-\text{norpregna-1,3,5(10)-trien-3-ol,}
\text{as well as its addition salts with acids.}
\]

Also a subject of the invention is a preparation process for the products of formula (I) as defined previously and characterized in that the product of formula (II):
in which $R_3$ has the same meaning as previously, if appropriate, is subjected to the action of an acylation or alkylation agent, in order to obtain the product of formula (IIA):

\[
\text{(IIA)}
\]

in which $R_3$ has the same meaning as previously, and $R'_5$ has the same meanings as $R_5$ as defined previously with the exception of hydrogen, and the product of formula (II) or (IIA) is subjected to the action of a cyanidation agent, in order to obtain the product of formula (III):

\[
\text{(III)}
\]

in which $R_3$ and $R_5$ have the same meanings as previously and in which the wavy line indicates that the product is presented in the form of pure stereoisomers (17alpha-OH, 17beta-CN) or (17alpha-CN, 17beta-OH) or in the form of a mixture, which is subjected to a dehydration reaction in order to obtain the product of formula (IV):

\[
\text{(IV)}
\]
in which \( R_3 \) and \( R_5 \) have the same meanings as previously, which is subjected to a reduction reaction of the 16-17 double bond, in order to obtain the product of formula (V):

\[
\text{(V)}
\]

in which the wavy line indicates that the CN substituent is in position 17alpha or 17beta, or in the form of a 17alpha and 17beta mixture, and \( R_3 \) and \( R_5 \) have the same meanings as previously, which is subjected to the action of an organometal reagent derived from the radical \( R_4 \) as defined previously, then to the action of an acid hydrolysis reagent, in order to obtain the product of formula (VI):

\[
\text{(VI)}
\]

in which \( R_3, R_4 \) and \( R_5 \) have the same meanings as previously and in which the wavy line indicates that the \( \text{COR}_4 \)
substituent is in position 17alpha or 17beta, or in the form of a 17alpha and 17beta mixture, which is subjected to the action of a hydroxylamine salt in order to obtain the product of formula (VII):

\[
\text{R}_3 \text{R}_4 \text{R}_5 \quad \text{(VII)}
\]

in which \( \text{R}_3, \text{R}_4 \) and \( \text{R}_5 \) have the same meanings as previously and in which the wavy line indicates that the \( \text{C} (\text{R}_4) = \text{N} - \text{OH} \) substituent is in position 17alpha or 17beta, or in the form of a 17alpha and 17beta mixture, and the oxime is in syn or anti position, or in the form of a syn and anti mixture, which is subjected to a reduction reaction of the oxime, in order to obtain the product of formula (VIII):

\[
\text{R}_3 \text{R}_4 \text{R}_5 \quad \text{(VIII)}
\]

in which the wavy line indicates that the \( \text{NH}_2 \) substituent is in position 20R or 20S, or in the form of a 20R and 20S mixture, and in which \( \text{R}_3, \text{R}_4 \) and \( \text{R}_5 \) have the same meanings as previously, which is subjected to the action of an acyl halide of formula:

\[
\text{X} - \text{CO} - (\text{CH}_2)_n' - \text{NR}_1 \text{R}_2
\]

in which \( \text{X} \) represents a halogen atom, \( \text{R}_1 \) and \( \text{R}_2 \) are as
defined previously, \( n' \) is equal to \( n-1 \), \( n \) being defined as previously, then, if appropriate, to a selective hydrolysis in position 3 of the diacylated compound formed intermediately, in order to obtain the product of formula (IX):

\[
\begin{align*}
R_1 &\quad R_2 \\
R_3 &\quad R_4 \\
R_5 &\quad n'
\end{align*}
\]

in which the wavy lines, \( R_1, R_2, R_3, R_4, R_5 \) and \( n' \) have the same meanings as previously, which is subjected to a reduction reaction of the keto group of the amide, then if desired and if necessary, to one or more of the following reactions in any order:

- acylation in position 3,
- alkylation in position 3,
- saponification of the acyloxy group in position 3,
- separation of the different stereoisomeres,
- salification by the action of a salt of an organic or mineral acid.

The acylation agent is preferably a carboxylic acid derivative, for example a chloride or an anhydride in the presence of a base such as pyridine.

The optional alkylation is carried out according to the usual methods. An alkylation agent is used which is preferably an alkyl halide such as an alkyl iodide or an alkyl sulphate.

The cyanidation agent is preferably sodium or potassium cyanide. This cyanidation reaction is preferably carried out in a lower alcohol such as methanol in the presence of acetic acid.

The dehydration reaction can be carried out using a dehydration agent such as phosphorus oxychloride in pyridine.
The reduction reaction of the 16-17 double bond can be carried out either by catalytic hydrogenation, the hydrogenation agent being hydrogen in the presence of catalysts such as palladium on charcoal, or a rhodium reagent such as Wilkinson reagent, or by the action of sodium borohydride in ethanol, or by the action of magnesium in methanol.

This reduction is either stereospecific and allows the CH substituent to be obtained in position 17alpha or in position 17beta, or it is non-stereospecific. Then a mixture of stereoisomers (17alpha + 17beta) is obtained which is separated, if appropriate, by standard methods such as crystallization or chromatography.

The organometal reagents which are derivatives of the R₄ radical are standard reagents, that-is-to-say an organolithium compound (R₄-Li), an organomagnesium compound (R₄-Mg-X), X being a halogen chosen from Cl, Br and I. It is preferably Br.

The acid hydrolysis reaction which follows the reaction with the organometal, allows the imine formed intermediately to be hydrolyzed. This hydrolysis is carried out under standard conditions for imine hydrolysis, in an acid medium such as hydrochloric acid, oxalic acid or acetic acid.

Formation of the oxime of formula (VII) is preferably carried out by the action of hydroxylamine hydrochloride in the presence of a base such as pyridine, soda or sodium carbonate.

The reduction reaction of the product of formula (VII) can be carried out by different methods such as catalytic hydrogenation with, as hydrogenation reagent, hydrogen in the presence of catalysts such as palladium on charcoal or platinum dioxide, by the action of zinc in an acetic medium, by sodium in an alcohol such as ethanol or n-propanol, or also by the addition of diborane in diglyme.

This reduction is either stereospecific and allows the product in position 20R or in position 20S to be obtained, or it is non-stereospecific. Then a mixture of 20R+20S stereoisomers is obtained which is separated, if appropriate,
by standard methods such as crystallization or chromatography.

The condensation of the compound of formula X-CO-(CH₂)n'-NR₁R₂, in which X is a halogen chosen from Cl, Br and I and n', R₁ and R₂ are as described previously, on the compound of formula (VIII) is carried out in a basic medium preferably in an aprotic dipolar solvent such as dimethyl-formamide (DMF). The reaction is preferably carried out in a triethylamine/dimethylformamide (TEA/DMF) medium.

The selective hydrolysis of the O-acyl compound which is optionally formed intermediately, is carried out under the usual conditions using an agent which can be an alkaline base such as soda or potash in a lower alcohol such as methanol or ethanol.

The reduction of the keto group of the amide of the compound of formula (IX) is carried out for example by means of a metal hydride such as lithium aluminium hydride (AlLiH₄) in an aprotic polar solvent such as tetrahydrofuran (THF) or ether, or by means of alkaline borohydrides such as sodium borohydride (NaBH₄) in the presence of acids such as acetic acid.

If desired and if necessary, the acylation or alkylation reactions of the -OH group in position 3 are carried out by the methods as described previously.

The saponification reaction, if desired and if necessary, is preferably carried out in the presence of an alkaline base such as soda or potash, potassium tertbutylate or lithium acetylide in ethylene amine. The saponification reaction takes place, preferably, in a lower alcohol, such as methanol or ethanol.

Separation, if desired and if necessary, of the different stereoisomers, is carried out according to standard methods of crystallization or chromatography.

The salification by an acid is carried out under the usual conditions. The operation is preferably carried out with hydrochloric acid, for example in an ethereal solution.

During the action of a cyanidation agent leading to the product of formula (III), of an organometal reagent leading
to the product of formula (VI) or of the hydroxylamine salt leading to the product of formula (VII), a product of formula (III), (VI) or (VII) can be obtained in which the acyloxy group is hydrolyzed.

5 The invention extends to a process as defined previously in which the product of formula (III), (VI) or (VII), in which the acyloxy group has been hydrolyzed, is reacylated if appropriate.

The products of formulae (V), (VI), (VII), (VIII) and (IX) are optionally obtained in the form of a mixture of stereoisomers. These products are, if desired or if necessary, subjected to operations which separate these stereoisomers.

Therefore the invention extends to a process as defined previously in which the different stereoisomers obtained during preparation processes of the products of formulae (V), (VI), (VII), (VIII) and (IX) are, if appropriate, separated.

The products of the invention have

1) a strong affinity for the Sigma receptors (see the pharmacological tests)

2) an activity vis-à-vis the influx of the calcium into the spermatozoid.

The results of tests show that among the products which fix to the Sigma receptors, certain act by stimulating the influx of calcium into the spermatozoid, others by inhibiting the influx of calcium stimulated or not by progesterone, a molecule described as binding to the Sigma receptor.

These properties justify their use in therapeutics and a subject of the invention is also, as medicaments, the products as defined by formula (I) above, as well as their addition salts with pharmaceutically acceptable acids.

A particular subject of the present invention is, as medicaments, the products corresponding to formula (I') as defined previously as well as their addition salts with pharmaceutically acceptable acids.

A more particular subject of the present invention is, as medicaments, the following compounds of general formula
Among the medicaments of the invention there can be mentioned quite particularly the following compound of general formula (I):

The products of formula (I), having an agonist activity, stimulate the influx of calcium into the spermatozoid. The corresponding medicaments according to the invention can be used in the treatment of certain forms of sterility characterized by an insufficient fertilizing power of the spermatozoids.

The products of formula (I) having an antagonist activity, inhibit the influx of calcium into the spermatozoid. The corresponding medicaments according to the invention are therefore of potential use in controlling the acrosomal reaction and consequently affect the fertilizing power of the spermatozoid. They can therefore be used as a contraceptive and in particular as a male contraceptive.

They can also be used in the veterinary domain as a male contraceptive in domestic animals (dogs, cats ...) or to limit the proliferation of any pests, in particular rodents or pigeons.

The useful dose varies as a function of the illness to be treated and the administration route. It can vary for example from 10 to 1000 mg per day in an adult by oral route.
The invention extends to the pharmaceutical compositions containing as active ingredient at least one medicament as defined above.

The compounds of formula (I) are used by digestive, parenteral or local route, for example by percutaneous route in particular for a woman, or by injection, in particular sub-cutaneous, in the veterinary domain. They can be prescribed in the form of plain or sugar-coated tablets, capsules, granules, suppositories, injectable preparations, pessaries and in particular vaginal pessaries, ointments, creams, gels, microspheres, implants, patches, which are prepared according to the usual methods.

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

Also a subject of the invention is as new industrial products useful, in particular in the implementation of the process according to the invention, the products of formulae (IIA), (III), (IV), (V), (VI), (VII), (VIII) and (IX), with the exception of the products of formula (IIA) in which R'₂⁵ is an alkyl group containing at most 12 carbon atoms.

The product of formula (II) is accessible according to the processes described in the following references:

The following example illustrates the invention without however limiting it.

**EXAMPLE 1:** (20S) (8alpha,9beta,13alpha,14beta,17alpha) 20-
((dimethylamino) ethyl)-amino 19-norpregna-1,3,5(10)-trien-3-
ol.

**Stage A:** 8alpha,9beta,13alpha,14beta 3-acetyloxy-estra-1,3,5
(10)-trien-17-one.

33.5 ml of acetic anhydride is added to a suspension of
33.3 g of antipodal estrone (preparation described in J.H. HUTCHINSON et al. Tetrahedron Letters 1985 26(15) p. 1819-1822) in 67 ml of pyridine. A slightly exothermic dissolution is observed, the temperature rising from 18°C to 32°C.

Agitation is carried out for 18 hours at 18 ± 2°C then the whole is poured into a mixture of ice-cooled water (660 ml)/22°Be hydrochloric acid (76 ml). After crystallization, the suspension is left at rest for 1 hour, filtered, washed with water and dried. 38.7 g of expected crude product is obtained which is purified by hot and cold recrystallization from 83 ml of absolute alcohol, followed by treatment with L2S activated charcoal, and after filtration and drying 32.7 g of desired product is obtained (M.p. = 128°C).

Stage B: (8alpha,9beta,13alpha,14beta,17beta)-3-(acetyloxy) 17-hydroxy-estra-1,3,5(10)-triene-17-carbonitrile.

91.6 g of potassium cyanide is introduced into a solution under an inert gas of 32.7 g of estrone acetate prepared according to Stage A, in 654 ml of methanol and 167 ml of acetic acid, and agitation is carried out for 16 hours at ambient temperature. Then 330 ml of an ice-water mixture is added to the suspension. After significant crystallization has been observed, the reaction medium is poured into 3 litres of ice-cooled water, followed by filtering and washing with water. The undried crude product is redissolved in 1.2 litres of ethyl acetate, the organic phase is washed, dried, filtered and concentrated until crystallization. After cooling down to -10°C for 1 hour, filtering is carried out followed by washing and drying. 27.2 g of expected product is obtained (M.p.= 198-200°C).

Stage C: (8alpha,9beta,13alpha,14beta) 3-hydroxy estra-1,3,5(10),16-tetraene-17-carbonitrile.

27.2 g of the product obtained in Stage B in 82 ml of pyridine and 25 ml of phosphorus oxychloride is heated under reflux for 4 hours. Then the reaction medium is cooled down to 20°C and poured over 450 ml of crushed ice. After an exothermic precipitation has been observed, sulphuric acid diluted to 1/5 is added in order to obtain a pH close to 1. Extraction is carried out with ethyl acetate, followed by
washing with water then with a solution of sodium bicarbonate, drying, filtering and evaporating to dryness under reduced pressure. The residue is redissolved in 60 ml of ethanol, then maintained under agitation for 1 hour at 0°C, followed by filtering and drying. 17.7 g of expected product is obtained (M.p. = 120°C).

Stage D: (8α,9β,13α,14β,17α) 3-hydroxy estra-1,3,5(10) triene-17-carbonitrile.

1.425 litres of hydrogen is introduced over 14 minutes into a suspension under nitrogen of 17.7 g of the product obtained in Stage C in 354 ml of ethyl acetate and 8.85 g of 10% palladium hydroxide on charcoal and agitation is carried out for 30 minutes. After filtering and evaporating to dryness under reduced pressure, the dry extract is redissolved in 90 ml of ethanol, agitated for one hour at a temperature of -10°C, followed by separation and drying.

15.35 g of expected product is obtained (M.p. = 144.5°C; (α)D = -100° (c = 1% CHCl₃)).

Stage E: (8α,9β,13α,14β,17α) 3-hydroxy-19-norpregna-1,3,5(10)-triene-20-one.

121 ml of methyl iodide is added under reflux over one hour to a mixture, under inert gas, of 46 g of magnesium turnings in 307 ml of benzene and 307 ml of ether. The reaction medium is heated under reflux for 30 minutes and a solution, prepared extemporaneously, of 15.35 g of the product obtained in Stage D in 154 ml of benzene and 154 ml of ether is introduced. Agitation is carried out under reflux for 93 hours. Reflux is stopped and the suspension is slowly poured into a water/ice mixture, and 340 ml of acetic acid (pH = 4) is added. After concentration, separation is carried out followed by washing and drying. 13.7 g of crude product is obtained which is purified in 840 ml of acetone and 0.6 g of 3SA activated charcoal, filtered, concentrated to 5 vol., agitated for one hour at a temperature of -10°C, separated and dried. 12.2 g of expected product is obtained (M.p. = 248°C, (α)D = -156.6° (c = 0.5% CHCl₃)).

Stage F: (8α,9β,13α,14β,17α) 20-
hydroxyimino-19-norpregna-1,3,5(10)-trien-3-ol.

4.5 g of hydroxylamine hydrochloride is added to a solution, under nitrogen, of 10 g of the product obtained in Stage E, in 100 ml of pyridine and the whole is heated to 80-85°C for 1 hour 30 minutes. Then 310 ml of demineralized water is added and crystallization of the product is observed, the crystals are separated out and recrystallized from 120 ml of ethanol under reflux. Another 75 ml of demineralized water is added and significant crystallization of the product is observed. Agitation is carried out for 30 minutes at 0°C, followed by separation and drying. 9.45 g of expected product is obtained (M.p. = 234°C).

Stage G: (20S) (8alpha,9beta,13alpha,14beta,17alpha) 19-norpregna-1,3,5(10)-trien-3-ol.

7.35 g of the product obtained in Stage F in 550 ml (+368 ml for rinsing) of acetic acid is added to a suspension of 2.94 g of platinum dioxide in 304 ml of acetic acid and hydrogenation is carried out with a total absorbed volume of 1075 ml of hydrogen over 6 hours 30 minutes.

Obtaining the hydrochloride:

After filtration, concentration under reduced pressure is carried out until a dry extract is obtained which is taken up in an acid medium constituted by a mixture of 4.15 ml of hydrochloric acid in 53.5 ml of ethanol and 1.2 ml of water. 92 ml of ether is added to the obtained solution and agitation is carried out at 0°C for 1 hour, followed by separation and drying. The crude hydrochloride is recrystallized by dissolution under reflux in 50 ml of ethanol with 0.5% hydrochloric acid and agitation is carried out for 1 hour at 0+5°C followed by separation.

Obtaining the base:

140 ml of demineralized water is slowly added hot to a solution of the hydrochloride purified in a basic mixture constituted by 11 ml of triethylamine, 64 ml of ethanol and 27 ml of water under reflux, crystallization is observed, agitation is carried out for 1 hour at 0+5°C, followed by separation and drying. 3.77 g of the crude base is obtained which is purified by dissolution under reflux in 120 ml of
ethanol, concentration at normal pressure and under nitrogen to a volume of 40 ml, agitation for 1 hour at 0°+5°C, separation and drying. 3.285 g of expected product is obtained (M.p. = 235°C).

Stage H: (20S) (8alpha,9beta,13alpha,14beta,17alpha) 2-dimethylamino N-(3-hydroxy 19-norpregna-1,3,5(10)-trien-20-yl) acetamide.

12 g of the hydrochloride of N,N dimethyl glycine chloride is added rapidly to a solution under inert gas of the product obtained in Stage G in 91.5 ml of dimethylformamide and 28.4 ml of triethylamine, obtained at 80°C then cooled down to +5°C, followed by agitation for 3 hours and pouring into a saturated solution of 370 ml of sodium acid carbonate in 550 ml of ice + water. Agitation is carried out for 1 hour followed by extraction with 3 times 100 ml of dichloromethane and washing with water then with a solution of sodium bicarbonate, then with a solution of salt water. The organic solutions are united and concentrated under reduced pressure until a dry extract of 6 g is obtained.

The residue is taken up, under inert gas, in 37 ml of methanol and 11 ml of 5N soda, followed by agitation for 1 hour until total dissolution, 220 ml of demineralized water is added slowly, carbon dioxide (pH 8) is bubbled through, 14.7 ml of triethylamine is added, agitation is carried out for 15 minutes, followed by extraction with 250 ml then 100 ml of dichloromethane, washing with 5 times 100 ml of water, the organic solution is dried, treated on 3SA activated charcoal, filtered, concentrated under reduced pressure until a dry extract (oil) is obtained which is recrystallized by two entrainments with ethanol. 6.15 g of expected crude product is obtained which is dissolved under reflux in 80 ml of ethanol, treated with L2S activated charcoal, filtered, concentrated at normal pressure to a volume of 40 ml, crystallization is observed, 10 ml of water is added, agitation is carried out for 1 hour at 0°+5°C, followed by separation and drying. 3.03 g of expected product is obtained (M.p. = 226°C).

Stage I: (20S) (8alpha,9beta,13alpha,14beta,17alpha) 20-
3.03 g of the product obtained in Stage H is added, at a temperature of 20°C, to a suspension, under inert gas, of 1.845 g of lithium aluminium hydride and 5.25 g of aluminium chloride in 131 ml of tetrahydrofuran and the whole is taken to reflux for 24 hours. After cooling down to 0±5°C, 20 ml of ethyl acetate is added then 100 ml of a saturated solution of sodium chloride is added. The suspension is filtered, then successively taken up in a water/6N HCl mixture (80 ml/50 ml), filtered, taken up in 60 ml of 60% ethanol and 8 ml of triethylamine and filtered. Water is added to the solution, precipitation is observed, extraction is carried out with dichloromethane, followed by washing, drying, treating on L2S activated charcoal and concentration under reduced pressure until a dry extract of 1.9 g is obtained. This dry extract is dissolved under reflux in 60 ml of ethyl acetate and 4 drops of triethylamine for 15 minutes, then the solution is concentrated under reduced pressure until a volume of 30 ml is obtained, cooled down over 1 hour to 0±5°C, separated and dried. 1.03 g of expected product is obtained (M.p.=177°C, (alpha)D -80.6° (c=0.5% EtOH)). Analysis for: C24H38O7N2 = 370.56

% calculated: 77.78 10.34 7.56
% found : 77.9 10.3 7.4

PHARMACOLOGICAL TESTS

30 METHOD
Preparation of the human spermatozoids
The human sperm originates from healthy donors. The mobile spermatozoids are separated by centrifugation on a Percoll gradient (47.5-95%) then resuspended in a hypertonic BWW medium containing: 166 mM NaCl, 5 mM KCl, 1.3 mM CaCl2, 1.2 mM KH2PO4, 1.2 mM MgSO4, 5.5 mM glucose, 21 mM sodium lactate, 0.25 mM sodium pyruvate, 25 mM NaHCO3, 20 mM Hepes and 0.8% of HSA (410 mosm/litre), pH 7.4 at ambient
temperature.

**Measurement of the intracellular calcium**

The mobile spermatozoids are incubated for a minimum of 2 hours in the BWW/HSA capacitating medium. They are then incubated (at a concentration of 5-10 x 10^6/ml) with Fura2-AM (final concentration 2 uM) at 37°C for 45 minutes. After washing (by centrifugation) at 600 g for 10 minutes in BWW without HSA, the spermatozoids are resuspended at a concentration of 4 x 10^6/ml. The fluorescence signal is measured at 37°C using a spectrofluorimeter at excitation wavelengths of 340 and 380 nm (PTIM 2001-Kontron) or at 340, 360 and 380 nm (Hitachi F 2000 - B. Braun Science Tec.). The fluorescence emission is recorded at 505 nm. The progesterone or the products to be tested, dissolved in absolute ethanol, are added to the incubation medium at a final concentration of 0.1% of ethanol. When an antagonistic effect of the progesterone is sought, the product is added to the medium 2 minutes before the progesterone. At the end of each dosage, 5 uM of ionomycin is added to the sample in order to measure the maximum fluorescence signal; then the spermatozoids are permeabilized with 0.05% of Triton X-100 and 10 mM of EGTA is added (pH 9.5) in order to measure the minimum fluorescence signal. These values allow the intracellular concentration of calcium ([Ca^{2+}]i) to be calculated according to the method described by Grunkiewicz et al (Grunkiewicz G., Poenie M. and Tsien R.Y. (1985) J. Biol. Chem. 260, 3440-3450). The results of the intracellular calcium concentrations are expressed relative to the basal level which is arbitrarily set equal to 1.

**Sigma receptor: measurement of the relative bond affinity**

The relative bond affinity is evaluated for preparations of rat brain and testicle membranes.

**Preparation of the membranes:**

Male Sprague-Dawley rates originating from Iffa Credo and weighing approximately 200 g are used. The animals are sacrificed by decapitation, the brain and testicles are removed and homogenized in 10 to 25 volumes of 50 mM Tris-HCl buffer (pH 7.7) at 4°C, using an Ultrathurax.
homogenates are centrifuged at 30,000 g for 15 minutes at 4°C, the pellets are then washed 3 times by resuspension (in the same buffer) and centrifugation under the same conditions. The membranes obtained in this way are stored at -80°C.

**Incubation:**

The marker of the sigma receptors used is $^3$H PPP (propyl-3-(3-hydroxyphenyl) piperidine) of NEN having a specific activity of 3404 GBq/mmol.

The membranes are resuspended in the 50 mM Tris-HCl buffer, pH 8.0 so as to obtain a concentration of proteins of approximately 0.6 mg/ml for the testicles and 1 mg/ml for the brain. Aliquots of the homogenate are incubated for 90 minutes at 25°C (in a total volume of 0.5 ml) with 3nM of $^3$H PPP in the presence of increasing concentrations of reference product (haloperidol) or of the products to be tested. At the end of the incubation, the $^3$H PPP bound to the membranes is separated from the free $^3$H PPP by rapid filtration on Whatman GF/C filters pre-treated beforehand with 0.05% of polyethyleneimine. The precipitate is then washed twice with 5 ml of Tris-HCl buffer. The radioactivity is counted after the addition of 20 ml of Aqualyte scintillating liquid (Baker).

**Calculation of the relative bond affinity (RBA):**

The following two curves are drawn: percentage of bound tritiated marker $100 \times \frac{B}{BO}$ as a function of the logarithm of the concentration of unlabelled reference product or as a function of the logarithm of the concentration of unlabelled test product.

The straight line of the following equation is determined:

$I_{50} = 100\left(\frac{BO}{BO+B_{\text{min}}/BO}\right)/2$ i.e.

$I_{50} = 100\left(1+B_{\text{min}}/BO\right)/2 = 50\left(1+B_{\text{min}}/BO\right)$

$BO$ = concentration of the bound tritiated marker in the absence of any unlabelled product.

$B = $ concentration of the bound tritiated marker in the presence of a concentration $X$ of unlabelled product.

$B_{\text{min}} = $ concentration of the bound tritiated marker in the presence of a large excess of the unlabelled reference product.
product (5,000 nM).

The intersections of the straight line I50 and the curves allow the evaluation of the concentrations of the unlabelled reference product (CH) and of the unlabelled test product (CX) which inhibit by 50% the specific binding of the tritiated marker on the receptor. The relative bond affinity (RBA) of the test product is determined by the equation:

\[ \text{RBA} = 100 \frac{(\text{CH})}{(\text{CX})}. \]

The RBA of the haloperidol is arbitrarily set equal to 100.

**PHARMACOLOGICAL TESTS**

1- Relative bond affinity (RBA) for the Sigma receptor

<table>
<thead>
<tr>
<th>Product</th>
<th>Brain (rat)</th>
<th>Testicle (rat)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ref: Haloperidol</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>Progesterone</td>
<td>0.7</td>
<td>0.3</td>
</tr>
<tr>
<td>Estrone</td>
<td>&lt; 0.06</td>
<td>&lt; 0.1</td>
</tr>
<tr>
<td>Product of Example 1 (product U)</td>
<td>4.3</td>
<td>58.0</td>
</tr>
</tbody>
</table>

2 - Measurement of intracellular calcium

Effect of progesterone at $10^{-5}\text{M}$ after 2 minutes of pre-treatment with product U, at different doses $10^{-8}\text{M}$ to $10^{-5}\text{M}$ on $[\text{Ca}^{2+}]_i$ Mean ± SEM $n = 3$

<table>
<thead>
<tr>
<th>PROG.</th>
<th>U10^{-8}M</th>
<th>U10^{-7}M</th>
<th>U10^{-6}M</th>
<th>U10^{-5}M</th>
</tr>
</thead>
<tbody>
<tr>
<td>alone</td>
<td>+ PROG.</td>
<td>+ PROG.</td>
<td>+ PROG.</td>
<td>+ PROG.</td>
</tr>
<tr>
<td>3.67±0.97</td>
<td>3.33±0.87</td>
<td>4.26±1.93</td>
<td>2.63±0.57</td>
<td>1.0±0.0</td>
</tr>
</tbody>
</table>
The results are expressed relative to the basal level set equal to 1.
Value of the basal level in the three experiments 176.70±22.90 nM.

Antagonistic effect of the product of the example at $10^{-5}$M on the effect of PROG at $10^{-5}$M. Mean ± SEM n = 8

<table>
<thead>
<tr>
<th></th>
<th>PROG. 10^{-5}M alone</th>
<th>U10^{-5}M alone</th>
<th>Pre-treatment 2 mn with U10^{-5}M + PROG. 10^{-5}M</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5.76 ± 0.84</td>
<td>0.95 ± 0.05</td>
<td>0.95 ± 0.05</td>
</tr>
</tbody>
</table>

The results are expressed relative to the basal level set equal to 1.

**CONCLUSION:**

**Effect on the intracellular calcium of human spermatozoids**

Progesterone at the concentration of $10^{-5}$ M induces a transitory increase of the $[Ca^{2+}]_i$ followed by a second phase where the $[Ca^{2+}]_i$ is slightly greater than the basal level.

As for the product of the example (at $10^{-5}$M), it completely antagonizes the effect of progesterone when it is added to the medium 2 minutes before the progesterone.

Relative bond affinity (RBA) for the sigma receptor

This product, and progesterone, are capable of displacing $^3$H PPP. The RBA's calculated using rat brain membranes have also been evaluated on testicles and are given in the table.

The differences observed between the RBA's at the level of the brain and testicles could be explained by a different distribution of the various types of sigma receptor sites between these two organs.

Such products could therefore inhibit the acrosomal reaction (essential stage of fertilisation) in the case of...
antagonists such as the product of the Example 1 and could therefore be used as a male contraceptive.
The claims defining the invention are as follows:

1) The compounds of formula (I):

\[
\text{SR}^1/\text{R}^2\text{C}_1\text{N}_{\text{R}^2}(\text{CH}_2)_n\text{N}_{\text{R}^3}\text{R}^4\text{R}^5
\]

in which \(\text{R}^1\) and \(\text{R}^2\), identical or different, represent an alkyl radical containing 1 to 12 carbon atoms, an aralkyl radical having 7 to 15 carbon atoms, or form together with the nitrogen atom to which they are linked a saturated heterocycle with 5 or 6 members optionally containing another heteroatom chosen from oxygen, nitrogen and sulphur, \(\text{R}^3\) in alpha position represents an alkyl radical containing 1 to 8 carbon atoms, \(n\) designates an integer comprised between 2 and 15, \(\text{R}^4\) represents an alkyl radical containing 1 to 12 carbon atoms, \(\text{R}^5\) represents a hydrogen atom, an acyl group containing at most 12 carbon atoms or an alkyl radical containing at most 12 carbon atoms, and the wavy lines indicate that the asymmetrical centres 17 and 20 can be independent of the absolute R or S configuration, as well as their addition salts with acids.

2) The compounds of general formula (I) as defined in claim 1, in which \(n\) is equal to 2, as well as their addition salts with acids.

3) The compounds of general formula (I) as defined in claim 1, corresponding to general formula (I'): 

\[
\text{SR}^1/\text{R}^2\text{C}_1\text{N}_{\text{R}^2}(\text{CH}_2)_n\text{N}_{\text{R}^3}\text{R}^4\text{R}^5
\]
in which $R_1$ and $R_2$ have the same meaning as previously, as well as their addition salts with acids.

4) The compounds of formula (I) as defined in claim 1, the names of which follow:

(20R) $(8\alpha, 9\beta, 13\alpha, 14\beta, 17\alpha)$ 20-(((dimethylamino) ethyl) amino) 19-norpregna-1,3,5(10)-trien-3-ol,

(20S) $(8\alpha, 9\beta, 13\alpha, 14\beta, 17\alpha)$ 20-(((dimethylamino) ethyl) amino) 19-norpregna-1,3,5(10)-trien-3-ol,

(20R) $(8\alpha, 9\beta, 13\alpha, 14\beta, 17\alpha)$ 20-(((dimethylamino) ethyl) amino) 19-norpregna-1,3,5(10)-trien-3-ol,

(20S) $(8\alpha, 9\beta, 13\alpha, 14\beta, 17\alpha)$ 20-(((dimethylamino) ethyl) amino) 19-norpregna-1,3,5(10)-trien-3-ol,

as well as their addition salts with acids.

5) The compound of formula (I) as defined in claim 1, the name of which follows:

(20S) $(8\alpha, 9\beta, 13\alpha, 14\beta, 17\alpha)$ 20-(((dimethylamino) ethyl) amino) 19-norpregna-1,3,5(10)-trien-3-ol,

as well as its addition salts with acids.

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

in which $R_3$ has the same meaning as in claim 1, if
appropriate, is subjected to the action of an acylation or alkylation agent, in order to obtain the product of formula (IIa):

\[ \text{(IIa)} \]

in which \( R_3 \) has the same meaning as previously, and \( R'_5 \) has the same meanings as \( R_5 \) as defined in claim 1, with the exception of hydrogen, and the product of formula (II) or (IIa) is subjected to the action of a cyanidation agent, in order to obtain the product of formula (III):

\[ \text{(III)} \]

in which \( R_3 \) and \( R_5 \) have the same meanings as previously and in which the wavy line indicates that the product is presented in the form of pure stereoisomers (17alpha-OH, 17beta-CN) or (17alpha-CN, 17beta-OH) or in the form of a mixture, which is subjected to a dehydration reaction in order to obtain the product of formula (IV):

\[ \text{(IV)} \]

in which \( R_3 \) and \( R_5 \) have the same meanings as previously, which is subjected to a reduction reaction of the 16-17 double bond, in order to obtain the product of formula (V):
in which the wavy line indicates that the CN substituent is in position 17alpha or 17beta, or in the form of a 17alpha and 17beta mixture, and R3 and R5 have the same meanings as previously, which is subjected to the action of an organometal reagent derived from the radical R4 as defined in claim 1, then to the action of an acid hydrolysis agent, in order to obtain the product of formula (VI):

in which R3, R4 and R5 have the same meanings as previously and in which the wavy line indicates that the COR4 substituent is in position 17alpha or 17beta, or in the form of a 17alpha and 17beta mixture, which is subjected to the action of a hydroxylamine salt in order to obtain the product of formula (VII):
in which $R_3$, $R_4$, and $R_5$ have the same meanings as previously and in which the wavy line indicates that the $C(R_4) = N-OH$ substituent is in position $17\alpha$ or $17\beta$, or in the form of a $17\alpha$ and $17\beta$ mixture, and the oxime is in syn or anti position, or in the form of a syn and anti mixture, which is subjected to a reduction reaction of the oxime, in order to obtain the product of formula (VIII):

![VIII](image)

in which the wavy line indicates that the $NH_2$ substituent is in position $20R$ or $20S$, or in the form of a $20R$ and $20S$ mixture, and in which $R_3$, $R_4$, and $R_5$ have the same meanings as previously, which is subjected to the action of an acyl halide of formula:

$$X-CO-(CH_2)_{n'}-NR_1R_2$$

in which $X$ represents a halogen atom, $R_1$ and $R_2$ are as defined in claim 1, $n'$ is equal to $n-1$, $n$ being defined as in claim 1, then, if appropriate, to a selective hydrolysis in position 3 of the diacylated compound formed intermediately, in order to obtain the product of formula (IX):

![IX](image)
in which the wavy lines, R₁, R₂, R₃, R₄, R₅ and n' have the same meanings as previously, which is subjected to a reduction reaction of the keto group of the amide, then if desired and if necessary, to one or more of the following reactions in any order:
- acylation in position 3,
- alkylation in position 3,
- saponification of the acyloxy group in position 3,
- separation of the different stereoisomers,
- salification by the action of a salt of an organic or mineral acid.

7) As medicaments, the compounds of formula (I) as defined in claim 1, as well as the addition salts with pharmaceutically acceptable acids.

8) As medicaments, the compounds of formula (I) as defined in any one of claims 2 to 4, as well as the addition salts with pharmaceutically acceptable acids.

9) As a medicament, the compound of formula (I) as defined in claim 5, as well as the addition salts with pharmaceutically acceptable acids.

10) The pharmaceutical compositions containing at least one of the medicaments defined in any one of claims 7 to 9 as active ingredient.

11) As new industrial products, the products of formulae (IIₐ), (III), (IV), (V), (VI), (VII), (VIII) and (IX) as defined in claim 6, with the exception of the products of formula (IIₐ) in which R₅' is an alkyl group containing at most 12 carbon atoms.

12) All compounds, processes, medicaments, compositions or products substantially as herein described.
ABSTRACT

A subject of the invention is the compounds of formula (I):

\[
\text{R}_1 \text{CH}_2(\text{CH}_2)_n\text{NH}_2 \text{H}_i \text{R}_2 (I)
\]

in which \(\text{R}_1\) and \(\text{R}_2\), identical or different, represent an alkyl having 1 to 12 carbon atoms, an aralkyl having 7 to 15 carbon atoms, or form together with the nitrogen atom to which they are linked a saturated heterocycle with 5 or 6 members optionally containing another heteroatom chosen from oxygen, nitrogen and sulphur, \(\text{R}_3\) in alpha position represents an alkyl having 1 to 8 carbon atoms, \(n\) is comprised between 2 and 15, \(\text{R}_4\) represents an alkyl having 1 to 12 carbon atoms, \(\text{R}_5\) represents a hydrogen, an acyl containing at most 12 carbon atoms or an alkyl containing at most 12 carbon atoms, and the wavy lines indicate that the asymmetrical centres 17 and 20 can be independent of the absolute R or S configuration, as well as their addition salts, their preparation process, their use as medicaments, the pharmaceutical compositions containing them and the new intermediates obtained.