- the first day of your last period was 50 days or more ago,
- an ectopic pregnancy is suspected (the egg implanted in the tubes rather than in your womb),
- due to the need to use prostaglandins in combination with MIFEGYNE, you should not have the treatment if:
  - you have had a bad reaction or allergy to prostaglandins,
  - you suffer or have had cardiovascular problems such as: angina (chest pain due to coronary artery disease), Raynaud's syndrome or disease (circulatory problems in the limbs), cardiac rhythm problems, cardiac insufficiency, severe high blood pressure.

- **<u>For patients receiving MIFEGYNE for softening and dilatation of the cervix uteri prior to surgical termination of pregnancy</u>:**
  - if the diagnosis of pregnancy has not been definitely established by biological tests or by ultrasound,
  - if the first day of your last menstrual period was 84 days or more ago (according to the law in your country),
  - if an ectopic pregnancy is suspected.

- **<u>For use prior to prostaglandins for late termination of pregnancy for medical reasons</u>**, the contraindications to the treatment are those of the prostaglandin selected by your doctor to induce expulsion.

- **<u>For labour induction to expel a dead fetus</u>**

  Should you need prostaglandins to complete the effect of MIFEGYNE, you should be informed of the contraindications of the medicine which will be used *(you may ask further information to your physician).*

b) SPECIAL WARNINGS

MIFEGYNE and the prostaglandin analogues (as well as the follow-up of your treatment), can only be prescribed and administered for termination of pregnancy in accordance with the national legal requirements.

As a consequence, they can only be prescribed by a medical doctor and in a public or private hospital or centre (having approval to undertake terminations of pregnancies) in accordance with the national legal requirements.

The signature of an informed consent letter would certify that you have been fully informed about the medical method of termination of pregnancy with MIFEGYNE and a prostaglandin and of its risks.

Unless decided otherwise by your doctor, it is not advised to use MIFEGYNE if you suffer from:

- renal or liver insufficiency *(severe disease of the liver or of the kidneys)*,
- malnutrition.

1) For the medical alternative to surgical termination of pregnancy

This method requires your active involvement and you should be informed of the method's requirements:

- to combine treatment with another medicine (prostaglandin) to be administered at a second visit,
- to return to the clinic for a control visit (3rd visit) within 10 to 14 days after MIFEGYNE's intake in order to check for complete expulsion,
- to terminate the pregnancy by another surgical method in case of treatment failure.

In any case of a pregnancy occurring on a intra-uterine device, this device must be removed before administration of MIFEGYNE.

- Risks related to the method

Failures:

The medical method of pregnancy termination with MIFEGYNE and a prostaglandin does not lead to 100% success. Usually, the success rate is about 95%.

Bleeding:

You may experience sometimes heavy, and/or prolonged vaginal bleeding (up to 12 days after MIFEGYNE intake). Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

Therefore, the control visit is mandatory in order to check that the treatment has been successful and well tolerated. This visit may be repeated in case treatment failure is suspected.

Consequently, you will be advised not to travel far away from the prescribing center until the procedure is completed.

Due to the risk of heavy bleeding during the medical method of pregnancy termination, should you suffer from hemorrhagic disorders with hypocoagulability (congenital anomaly, etc...) or anemia, the decision to use the medical or the surgical method should be decided by your doctor.

2) For patients receiving MIFEGYNE for dilatation of the cervix uteri prior **to surgical termination of pregnancy**

For the full efficacy of therapy, the use of MIFEGYNE must mandatorily be followed, 36 to 48 hours later and not beyond, by surgical termination. A shorter or longer time lag may compromise the efficacy of the therapy.

3) In any case

The use of MIFEGYNE requires the prevention of rhesus allo-immunisation (if you are rhesus negative) as well as other general measures taken usually during any pregnancy termination.

It is possible for you to become pregnant again immediately after the termination is complete so you will need to start contraception as early as possible after taking the MIFEGYNE tablets. You should not be pregnant in the menstrual cycle following treatment.

c) PRECAUTIONS FOR USE

1) In any case

Due to specific properties of mifepristone, the efficacy of long-term corticosteroid therapy may be decreased during the 3 to 4 days following MIFEGYNE's intake.

Inform your doctor if you suffer from asthma and if you are taking cortisone treatment in order to have your treatment adjusted if needed.

If you take on a regular basis, non steroidal anti-inflammatory drugs including aspirin as these medications may decrease the method's efficacy.

Should you need to receive pain relief tablets because of painful uterine contractions, do not take any anti-inflammatory medication or aspirin without your doctor advice. You will be prescribed a more appropriate treatment if needed.

2) Medical alternative to surgical termination of pregnancy

As a special precautionary measure and due to rare serious cardiovascular accidents reported following the administration of a certain type of prostaglandin, the medical method is not recommended for use if you are over 35 years of age and smoke more than 10 cigarettes a day.

Method of prostaglandins administration.

During intake and for three hours following the intake, you will be monitored in the treatment centre, which must be equiped with the appropriate monitoring equipment.

3) **For the sequential use of MIFEGYNE – Prostaglandin, whatever the indication**

The precautions related to the prostaglandins used should be followed where relevant. You may ask your doctor for further information.

d) INTERACTIONS WITH OTHER MEDICINES

IN ORDER TO AVOID INTERACTION BETWEEN SEVERAL MEDICATIONS YOU SHOULD TELL YOUR DOCTOR OR YOUR PHARMACIST IF YOU ARE TAKING ANY KIND OF TREATMENT.

e) PREGNANCY - LACTATION

This method of termination of pregnancy may fail.

Therefore, the control visit is mandatory. In the event of failure you will be offered to terminate the pregnancy by another method.

Should the vaginal bleeding persist or in case the next period is missed, inform your hospital doctor *(or clinic)* as soon as possible in order to determine what to do on a case by case basis.

The risks to the fetus in case of an ongoing pregnancy are unknown. Should you change your mind and wish to continue your pregnancy, ask your doctor. You would be proposed prenatal care with repeated ultrasonographies.

There is not data available about MIFEGYNE's excretion in the mother's breast milk. MIFEGYNE use should be avoided during breast-feeding.

AS A GENERAL RULE, YOU SHOULD ALWAYS TELL YOUR DOCTOR OR YOUR PHARMACIST IF YOU ARE BREAST FEEDING BEFORE TAKING ANY MEDICATION.

f) EFFECTS ON ABILITY TO DRIVE AND TO USE MACHINES

Not known.

g) SPORT

Nothing prevents you from exercising unless the side-effects of the treatment make you feeling sick (see section 4).

3. HOW TO USE MIFEGYNE

a) Dosage

– For the medical termination of a developing intra-uterine pregnancy:

The following prescription will be written by your doctor and you should receive the medication in the presence of the doctor or the nurse or midwife.

- 3 tablets of MIFEGYNE to swallow with some water in a single dose.

As a practical guide:

1. After intake of MIFEGYNE, you may go home with another appointment 36 to 48 h. later. You will be given a phone number to use in case you need emergency medical help, especially in case of very heavy bleeding. Bleeding usually starts 1 or 2 days after intake of MIFEGYNE.

   Occasionally, the expulsion may take place before your next appointment for the prostaglandin intake. Nevertheless, complete expulsion must be verified and you must return to the centre for that control.

2. You must then return to the hospital or clinic 2 days later to be given the prostaglandin.

   After you are given the prostaglandin, you should rest at the hospital/clinic for about 3 hours and you can then go home. You will receive, if it is relevant, a prescription for a contraceptive method.

   The products of conception will be expelled during the hours when you will be at the clinic or within the following days. Bleeding usually persists until the follow-up visit.

3. You must return to the hospital/clinic for a mandatory follow-up visit 10 to 14 days after intake of MIFEGYNE. Should your pregnancy be still continuing or the expulsion be incomplete, an appropriate treatment will be prescribed.

   Therefore, you should not travel far away form the prescribing centre until the procedure is completed.

Obviously, if there is any cause for concern, you can either contact the hospital or return to the hospital or centre prior to the appointment time. You will be given a phone number to call in case of concern or emergency.

- For softening of the cervix uteri before surgical termination of pregnancy:

  As a practical guide:

  1. The treatment will consist of intake of one MIFEGYNE tablet by mouth, at the clinic in the presence of the doctor or the nurse.

  2. After administration of MIFEGYNE, you may go home with an appointment 36 to 48 hours later for the surgical procedure.
     Your doctor will explain this to you.
     You may experience vaginal bleeding after MIFEGYNE intake, before surgery. In rare instances, an expulsion may take place before the surgical procedure. You must return to the clinic to check that expulsion is complete.

  3. You will be given a phone number to reach in case of emergency *(or for medical support).*

  4. You must return to the clinic/hospital for the surgical procedure. After the surgery, you should stay and rest at the centre a few hours. You may then go home with, if relevant, a prescription for a contraceptive method.

- For termination of pregnancy for medical reasons:

  - 3 tablets of MIFEGYNE in a single dose in the presence of the doctor or the nurse or midwife,
  - you will be given an appointment to return to the hospital 36 to 48 hours (2 days) later to be given a prostaglandin which administration may be repeated until the termination has been completed.

- For labor induction to expel a dead fetus:

  3 tablets of MIFEGYNE daily for 2 consecutive days.

b) MODE AND ROUTE OF ADMINISTRATION

Oral route.

c) FREQUENCY AND TIME OF ADMINISTRATION OF THE MEDICATION

According to the medical prescription.

d) DURATION OF TREATMENT

MIFEGYNE is administered in a single dose (see above) but in the case of labor induction to expel a dead fetus, where the treatment is usually prescribed for 2 consecutive days.

e) **WHAT TO DO IN CASE YOU TAKE TOO MANY TABLETS**

According to the conditions of administration, an overdosage is very unlikely. However, any suggestion of acute intoxication requires treatment in a specialised environment.

f) **WHAT TO DO IN CASE ONE OR SEVERAL DOSES HAVE BEEN MISSED**

g) **AFTER-EFFECTS WHEN MIFEGYNE IS STOPPED**

None.

4. POSSIBLE SIDE-EFFECTS

AS WITH ANY MEDICATION, MIFEGYNE MAY, IN SOME PEOPLE, INDUCE ADVERSE REACTIONS.

- Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in about 1% of the women.

- Uterine contractions which are often painful, occur frequently: in 10 to 45% of the cases they occur in the hours following prostaglandin intake (The clinic will be able to give you appropriate pain killers).

- During therapeutic termination of pregnancy for medical reasons, rare cases of uterine rupture have been reported after prostagladin intake.
  The reports occurred particularly in multiparous women or in women with a cesarean section scar.

- Gastrointestinal side-effects such as nausea, vomiting, diarrhea are common after the prostaglandin administration.

- Rare cases of blood pressure decrease.

Other rare side-effects

- Allergy such as skin rash or urticaria, and other skin disorders. Headache, dizziness, fever.

IF YOU THINK YOU ARE REACTING BADLY IN ANY OF THESE OR ANY OTHER WAYS TO YOUR MEDICINE, PLEASE TELL YOUR DOCTOR OR PHARMACIST (NURSE) STRAIGHT AWAY.

5. STORING MIFEGYNE

You will not be asked to store your medicine.

- **Do not use the tablets after the expiry date stated on the box**
- **MIFEGYNE tablets must be stored at normal room temperature**
- **Do not use MIFEGYNE if you notice signs of damage to the box or tablets**

6. DATE OF REVISION OF THE LEAFLET

July 1999.

APPEARS THIS WAY
ON ORIGINAL

Appendix 4: European Summary of Product Characteristics, 6 July 1999, with cover letter of approval under the Mutual Recognition Procedures of the European Union.

APPEARS THIS WAY
ON ORIGINAL

AGENCE
FRANÇAISE DE SÉCURITÉ SANITAIRE DES
PRODUITS DE SANTÉ

DIRECTION DE L'EVALUATION
European Procedures Unit

Tel: 33 1 55 87 32 98
Fax: 33 1 55 87 32 92

(3)

Saint-Denis, 06 JUIL 1999

To: Dr Christa Wirthumer Hoche (Austria)
Mrs Natacha Grenier (Belgium)
Mrs Birgitte Kristensen (Denmark)
Dr Birka Lehman (Germany)
Mrs Sinikka Lauer (Finland)
Mrs J.Yotaki / V. Revithi (Greece)
Mrs J. Genoux-Hames (Luxemburg)
Mrs Truus Janse-de Hoog (Netherlands)
Dr Emili Esteve (Spain)
Cc: Mrs Sabine Haubenreisser (EMEA)
Cc: Mrs C. Basset - Exelgyn
Fax : 01 53 57 37 40

From : Dr Solange Rohou
Pharmaceutical assessors : Mrs Claire Clémencin / Mrs Anne Chardon
Clinical assessor: Dr Lise Duranteau

Re: MIFEGYNE 200mg, tablet
Mutual Recognition Procedure No.: FR/H/137/01

Dear colleagues,

For the above mentioned procedure, France as RMS, has received final comments from all Concerned Member States. These comments have been included in the updated SPC here within enclosed.

The 90-day period ended on July 5, 1999. Consequently, the procedure FR/H/137/01 is now considered as positively ended except in Luxemburg where the application has been withdrawn.

Concerned Member States are now asked to grant nationally the marketing authorisation within 30 days, subject to the receipt of the translations in national languages of the final version of the SPC.

Thank you for your kind co-operation
Best regards,

AGENCE
FRANÇAISE DE SÉCURITÉ SANITAIRE DES
PRODUITS DE SANTÉ
143-147, Boulevard Anatole France
93285 SAINT-DENIS CEDEX

Dr Solange Rohou
Mutual Recognition Procedures

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MIFEGYNE® 200 mg tablet

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 200-mg mifepristone.

3. PHARMACEUTICAL FORM

Tablet.
Light yellow, cylindrical, biconvex tablets marked "167 B" on one side.

4. CLINICAL PARTICULARS

For termination of pregnancy, MIFEGYNE® and the prostaglandin can only be prescribed and administered in accordance with the countries laws and regulations.

As a consequence, they can only be prescribed by a medical doctor and in public or private hospital or centre (having approval to undertake termination of pregnancy). The product will be administered in the presence of the medical practitioner or of a delegated health professional.

If required by the afore mentioned laws and regulations, the patient should sign a letter of informed consent to certify that she has been fully informed about the method and its risks.

This timing of the first visit should take into account the requirement of some countries for a period of reflection prior to the abortion procedure.

4.1 Therapeutic indications

1- **Medical termination of developing intra-uterine pregnancy.**

In sequential use with a prostaglandin analogue, up to 49 days of amenorrhea.

2- **Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester.**

3- **Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester).***

4- **Labour induction in foetal death in utero.**

In patients where prostaglandin or oxytocin cannot be used.

4.2 Posology and Method of Administration

1- Medical termination of developing intra-uterine pregnancy

The method of administration will be as follows:

600 mg of mifepristone (i.e. 3 tablets of 200 mg each) is taken in a single oral dose, followed by 36 to 48 hours later, the administration of a prostaglandin analogue; misoprostol 400 µg orally, or gemeprost 1 mg per vaginum.

2- Softening and dilatation of the cervix uteri prior to surgical termination of pregnancy during the first trimester

200 mg of mifepristone (one tablet), followed 36 to 48 hours later (but not beyond) by surgical termination of pregnancy.

3- Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons

600 mg of mifepristone (i.e. 3 tablets of 200 mg each) taken in a single oral dose, 36 to 48 hours prior to scheduled prostaglandin administration which will be repeated as often as indicated.

4- Labour induction in foetal death in utero

600 mg of mifepristone (e.g. 3 tablets of 200 mg each) in a single oral daily dose, for two consecutive days.

Labour should be induced by the usual methods if it has not started within 72 hours following the first administration of mifepristone.

4.3 Contra-indications

This product SHOULD NEVER be prescribed in the following situations.

<u>In all indications</u>

- chronic adrenal failure
- known allergy to mifepristone or to any component of the product
- severe asthma uncontrolled by therapy

<u>In the indication: medical termination of developing intra-uterine pregnancy</u>

- pregnancy not confirmed by ultrasound scan or biological tests
- pregnancy of 50 days' amenorrhea and beyond
- suspected extra-uterine pregnancy
- contra-indication to the prostaglandin analogue selected

In the indication: softening and dilatation of the cervix uteri prior to surgical termination of pregnancy:

- pregnancy not confirmed by ultrasound scan or biological test
- pregnancy of 84 days of amenorrhea and beyond (according to legal requirements)
- suspected extra-uterine pregnancy

Preparation for the action of prostaglandin analogues in the termination of pregnancy for medical reasons *(beyond the first trimester)*

- contra-indications to the prostaglandin analogue selected

Labour induction in foetal death in utero

Should prostaglandin combination be required, refer to contra-indications to the prostaglandin analogue selected.

4.4 Special warnings and special precautions for use

Warnings

In the absence of specific studies, MIFEGYNE® is not recommended in patients with:

- ***Renal failure***
- ***Hepatic failure***
- ***Malnutrition***

1- Medical termination of developing intra-uterine pregnancy

This method requires an active involvement of the woman who should be informed of the method's requirements:

- the necessity to combine treatment with prostaglandin to be administered at a second visit,
- the need for a control visit (3rd visit) within 10 to 14 days after MIFEGYNE's intake in order to check for complete expulsion,
- The possible failure of the method, leading to a pregnancy termination by another method.

In the case of a pregnancy occurring with an intra-uterine device in situ, this device must be removed before administration of MIFEGYNE®.

The expulsion may take place before prostaglandin administration (in about 3% of cases). This does not preclude the control visit in order to check for the complete expulsion and the uterine vacuity.

- Risks related to the method

  - Failures

    The non-negligible risk of failure, which occurs in 1.3 to 7.5 % of the cases, makes the control visit mandatory in order to check that the expulsion is completed.

  - Bleeding

    The patient must be informed of the occurrence of prolonged vaginal bleeding (up to 12 days after MIFEGYNE® intake) which may be heavy. Bleeding occurs in almost all cases and is not in anyway a proof of complete expulsion.

    The patient should be informed not to travel far away from the prescribing centre as long as complete expulsion has not been recorded. She will receive precise instructions as to whom she should contact and where to go, in the event of any problems emerging, particularly in the case of very heavy vaginal bleeding.

    A follow-up visit must take place within a period of 10 to 14 days after administration of MIFEGYNE® to verify by the appropriate means (clinical examination, ultrasound scan, and Beta-HCG measurement) that expulsion has been completed and that vaginal bleeding has stopped. In case of persistent bleeding (even light) beyond the control visit, its disappearance should be checked within a few days.

    If an ongoing pregnancy is suspected, a further ultrasound scan may be required to evaluate its viability.

    Persistence of vaginal bleeding at this point could signify incomplete abortion, or an unnoticed extra-uterine pregnancy, and appropriate treatment should be considered.

    In the event of an ongoing pregnancy diagnosed after the control visit, termination by another method will be proposed to the woman.

    Since heavy bleeding requiring hemostatic curettage occurs in 0 to 1.4% of the cases during the medical method of pregnancy termination, special care should be given to patients with hemostatic disorders with hypocoagulability, or with anemia. The decision to use the medical or the surgical method should be decided with specialised consultants according to the type of hemostatic disorder and the level of anaemia.

2- Softening and dilatation of the cervix uteri prior to surgical pregnancy termination

For the full efficacy of therapy, the use of MIFEGYNE® must be followed, 36 to 48 hours later and not beyond, by surgical termination.

- Risks related to the method

  - Bleeding

    The woman will be informed of the risk of vaginal bleeding which may be heavy, following MIFEGYNE's intake. She should be informed of the risk of abortion prior to surgery (although minimal): she will be informed on where to go in order to check for the completeness of expulsion, or in any case of emergency.

  - Other risks

    They are those of the surgical procedure.

3- in all instances

The use of MIFEGYNE® requires rhesus determination and hence the prevention of rhesus allo-immunisation as well as other general measures taken usually during any termination of pregnancy.

During clinical trials, pregnancies occurred between embryo expulsion and the resumption of menses.

To avoid potential exposure of a subsequent pregnancy to mifepristone, it is recommended that conception be avoided during the next menstrual cycle. Reliable contraceptive precautions should therefore commence as early as possible after mifepristone administration.

Precautions for use

1- in all instances

In case of suspected acute adrenal failure, dexamethasone administration is recommended. 1 mg of dexamethasone antagonises a dose of 400 mg of mifepristone.

Due to the antiglucocorticoid activity of mifepristone, the efficacy of long-term corticosteroid therapy, including inhaled corticosteroids in asthmatic patients, may be decreased during the 3 to 4 days following MIFEGYNE's intake. Therapy should be adjusted.
A decrease of the efficacy of the method can theoretically occur due to the antiprostaglandin properties of non-steroidal anti-inflammatory drugs (NSAIDs) including aspirin (acetyl salicylic acid). Use preferably non-NSAI analgesics.

2- Medical termination of developing intra-uterine pregnancy

Rare serious cardiovascular accidents have been reported following the intra muscular administration of the prostaglandin analogue sulprostone (withdrawn in 1992). No such cases have been reported since analogues of PGE_1 (gemeprost or misoprostol) have been used. For these reasons and as a special precautionary

measure, the medical method is not recommended for use in women over 35 years of age and who smoke more than 10 cigarettes a day.

Method of prostaglandin administration

During intake and for three hours following the intake, the patients should be monitored in the treatment centre, which must be equipped with the appropriate equipment.

3- **for the sequential use of MIFEGYNE® - Prostaglandin, whatever the indication**

The precautions related to the prostaglandin used should be followed where relevant.

4.5 Interaction with other medicinal products and other forms of interactions

No studies to investigate possible interactions between mifepristone and other drugs have been carried out.

4.6 Pregnancy and lactation

In animals (see section 5.3 Pre-clinical safety data), the abortifacient effect of mifepristone precludes the proper assessment of any teratogenic effect of the molecule.

With subabortive doses, isolated cases of malformations observed in rabbits, but not in rats or mice were too few to be considered significant, or attributable to mifepristone.

In humans, the few reported cases of malformations do not allow a causality assessment for mifepristone alone or associated to prostaglandin. Therefore, data is too limited to determine whether the molecule is a human teratogen.

Consequently:

- Women should be informed, that due to the risk of failure of the medical method of pregnancy termination and to the unknown risk to the foetus, the control visit is mandatory (see Section 4.4 special warnings and special precautions for use).
- Should a failure of the method be diagnosed at the control visit *(viable ongoing pregnancy)*, and should the patient still agree, pregnancy termination should be completed by another method.
- Should the patient wish to continue with her pregnancy, the available data is too limited to justify a systematic termination of an exposed pregnancy. In that event, a careful ultra-sonographic monitoring of the pregnancy will be established.

Lactation

Mifepristone is a lipophilic compound and may theoretically be excreted in the mother's breast milk. However, no data is available. Consequently, mifepristone use should be avoided during breast-feeding.

4.7 Effects on ability to drive and to use machines

Not known.

4.8 Undesirable effects

Most frequently reported undesirable effects

- Urogenital
  - Bleeding
    Heavy bleeding occurs in about 5% of the cases and may require hemostatic curettage in up to 1.4% of the cases.
  - Very common uterine contractions or cramping (10 to 45%) in the hours following prostaglandin intake.
  - During induction of second trimester termination of pregnancy or labour induction for foetal death in utero during the third trimester, uterine rupture has been uncommonly reported after prostaglandin intake. The reports occurred particularly in multiparous women or in women with a caesarean section scar.
- Gastrointestinal
  - Cramping, light or moderate.
  - Nausea, vomiting.
- Undesirable effects related to prostaglandin use: nausea, vomiting or diarrhoea, and rarely hypotension (0.25%)

Other undesirable effects

- Hypersensitivity and skin
  - Hypersensitivity: skin rashes uncommon (0.2%), single cases of urticaria.
  - Single cases of erythroderma, erythema nodosum, epidermal necrolysis have also been reported.
- Other systems
  Rare cases of headaches, malaise, vagal symptoms (hot flushes, dizziness, chills have been reported) and fever.

4.9 Overdose

After extensive clinical use, no reports of acute intoxication have been reported.

In the event of accidental massive ingestion, signs of adrenal failure might occur. Signs of acute intoxication may require specialist treatment including the administration of dexamethasone.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

OTHER SEX HORMONE AND MODULATOR OF THE REPRODUCTIVE FUNCTION/ ANTIPROGESTOGEN (GO3 X B01: Urogenital System and Sex Hormones).

Mifepristone is a synthetic steroid with an antiprogestational action as a result of competition with progesterone at the progesterone receptors.

At doses ranging from 3 to 10 mg/kg orally, it inhibits the action of endogenous or exogenous progesterone in different animal species (rat, mouse, rabbit and monkey). This action is manifested in the form of pregnancy termination in rodents.

In women at doses of greater than or equal to 1mg/kg, mifepristone antagonises the endometrial and myometrial effects of progesterone. During pregnancy it sensitises the myometrium to the contraction- inducing action of prostaglandin. During the first trimester, pre-treatment with mifepristone allows the dilatation and opening of the cervix uteri. While clinical data have demonstrated that mifepristone facilitates dilatation of the cervix, no data are available to indicate that this results in a lowering of the rate of early or late complications to the dilatation procedure.

In the event of an early termination of pregnancy, the combination of a prostaglandin analogue used in a sequential regimen after mifepristone leads to an increase in the success rate to about 95 per cent of the cases and accelerates the expulsion of the conceptus.

In clinical trials, according to the prostaglandin used and the time of application, the results vary slightly.

The success rate is up to 95.7% when misoprostol is used orally up to 49 days of amenorrhea, and with gemeprost applied vaginally, it reaches 98.7% up to 49 days of amenorrhea and 94.8% up to 63 days of amenorrhea.

According to the clinical trials and to the type of prostaglandin used, the failure rate varies. Failures occur in 1.3 to 7.5% of the cases receiving sequentially MIFEGYNE® followed by a prostaglandin analog, of which:

- 0 to 1.5% of ongoing pregnancies
- 1.3 to 4.6% of partial abortion, with incomplete expulsion
- 0 to 1.4% of hemostatic curettage

Combinations of mifepristone with other prostaglandin analogues have not been studied.

During the termination of pregnancy for medical reasons *beyond the first trimester*, mifepristone administered at a 600-mg dose, 36 to 48 hours prior to the first administration of prostaglandins, reduces the induction-abortion interval, and also decreases the prostaglandin doses required for the expulsion.

When used for labour induction of foetal death in utero, mifepristone alone induces expulsion in about 60% of cases within 72 hours following the first intake. In that event, the administration of prostaglandin or ocytocics would not be required.

Mifepristone binds to the glucocorticoid receptor. It doesn't bind to mineralocorticoid receptors; therefore, the risk of acute adrenal failure during mifepristone intake is negligible. In animals at doses of 10 to 25 mg/kg it inhibits the action of dexamethasone. In man the antiglucocorticoid action is manifested at a dose equal to or greater than 4.5 mg/kg by a compensatory elevation of ACTH and cortisol.

Mifepristone has a weak anti-androgenic action which only appears in animals during prolonged administration of very high doses.

5.2 Pharmacokinetic properties

After oral administration of a single dose of 600 mg mifepristone is rapidly absorbed. The peak concentration of 1.98 mg/l is reached after 1.30 hours (means of 10 subjects).

There is a non-linear dose response. After a distribution phase, elimination is at first slow, the concentration decreasing by a half between about 12 and 72 hours, and then more rapid, giving an elimination half-life of 18 hours. With radio receptor assay techniques, the terminal half-life is of up to 90 hours, including all metabolites of mifepristone able to bind to progesterone receptors.

After administration of low doses of mifepristone (20 mg orally or intravenously), the absolute bioavailability is 69%.

In plasma mifepristone is 98% bound to plasma proteins: albumin and principally alpha-1-acid glycoprotein (AAG), to which binding is saturable. Due to this specific binding, volume of distribution and plasma clearance of mifepristone are inversely proportional to the plasma concentration of AAG.

N-Demethylation and terminal hydroxylation of the 17-propynyl chain are primary metabolic pathways of hepatic oxidative metabolism.

Mifepristone is mainly excreted in faeces. After administration of a 600 mg labelled dose, 10% of the total radioactivity is eliminated in the urine and 90% in the faeces.

5.3 Preclinical safety data

In toxicological studies in rats and monkeys up to a duration of 6 months, mifepristone produced effects related to its antihormonal (antiprogesterone, antiglucocorticoid and antiandrogenic) activity.

In reproduction toxicology studies, mifepristone acts as a potent abortifacient. No teratogenic effect of mifepristone was observed in rats and mice surviving foetal exposure. In rabbits surviving foetal exposure, however, isolated cases of severe abnormalities occurred (cranial vault, brain and spinal cord). The number of foetal anomalies was not statistically significant and no dose-effect was observed. In monkeys, the number of foetuses surviving the abortifacient action of mifepristone was insufficient for a conclusive assessment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Colloidal silica anhydrous, maize starch, povidone, magnesium stearate, microcrystalline cellulose.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

3 years.

6.4 Special precautions for storage

None.

6.5 Nature and contents of container

3 tablets in blister (PVC / Aluminium).

6.6 Instructions for use and handling

Not applicable.

7. MARKETING AUTHORISATION HOLDER

EXELGYN
6, rue Christophe Colomb
75008 PARIS
France

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

Appendix 5: Copies of box labeling for France and the United Kingdom

APPEARS THIS WAY
ON ORIGINAL

Box Labeling for France

APPEARS THIS WAY
ON ORIGINAL

Box Labeling for United Kingdom

APPEARS THIS WAY
ON ORIGINAL

MIFEGYNE®

MIFEPRISTONE

Oral route

200 mg · 3 tablets

MIFEGYNE®

MIFEPRISTONE

200 mg

3 tablets

Exelgyn

LABORATOIRES

MIFEGYNE®

MIFEPRISTONE

Oral route

200 mg · 3 tablets

Use as directed by the physician.
See enclosed leaflet for indications, dosage, contra-indications, precautions and side effects.

KEEP OUT OF THE REACH OF CHILDREN

Store below 30°C.

The tablets must be taken in the presence of the prescribing physician

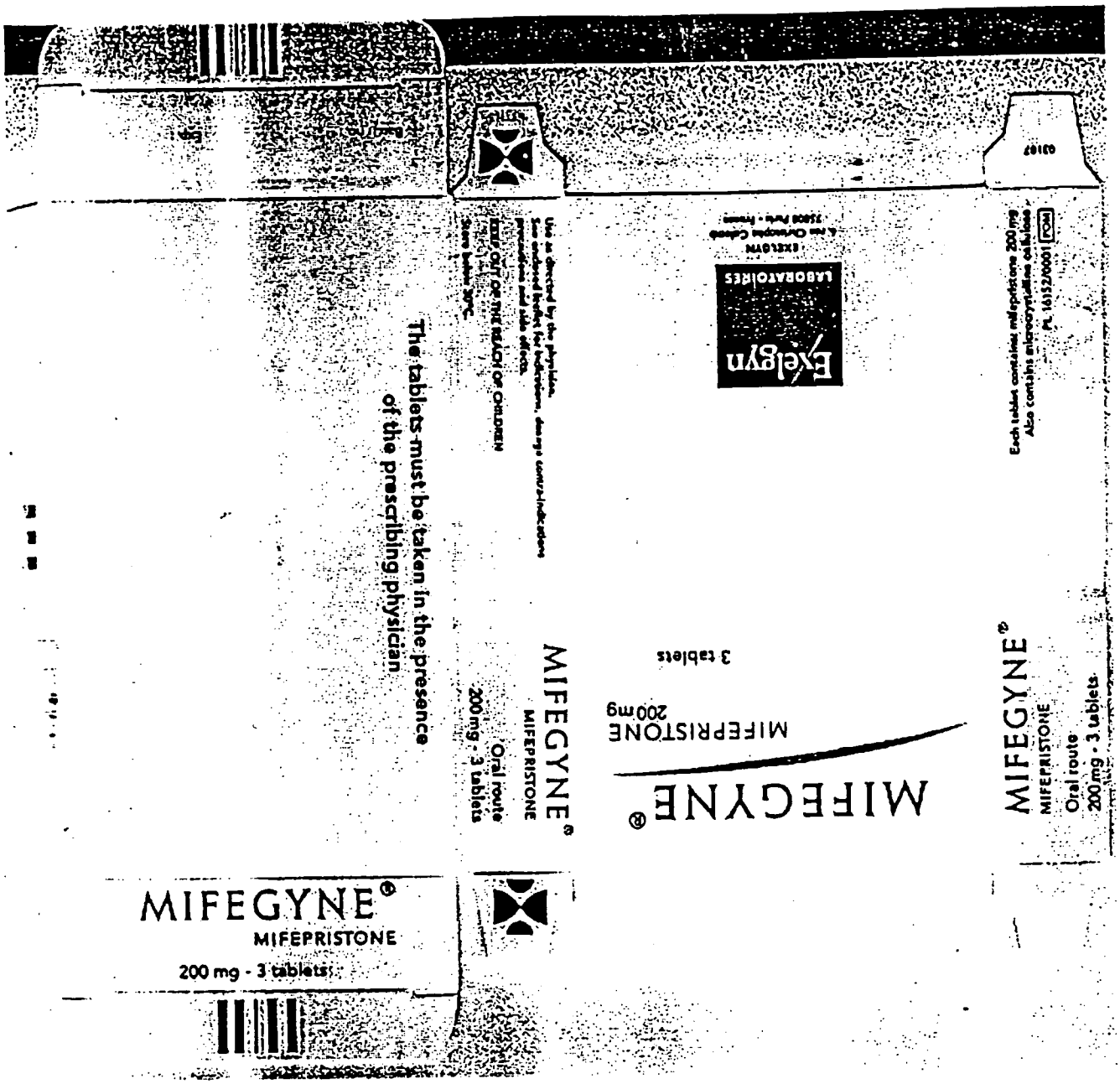
MIFEGYNE®

MIFEPRISTONE

200 mg - 3 tablets

MIF 003324

MIF 003325


MIFEGYNE®
MIFEPRISTONE
200 mg - 3 tablets
The tablets must be taken in the presence of the prescribing physician
MIFEGYNE®
MIFEPRISTONE
Oral route
200 mg - 3 tablets
Keep out of the reach of children
Store below 30°C
Use as directed by the physician.
See enclosed leaflet for indications, dosage, contraindications, precautions and side effects.
Exelgyn
LABORATOIRES
EXELGYN
4, rue Chrysippe Cahen
75008 Paris - France
Each tablet contains: mifepristone 200 mg
Also contains: microcrystalline cellulose,
PL 16152/0001
MIFEGYNE®
MIFEPRISTONE
200 mg
3 tablets
MIFEGYNE®
MIFEPRISTONE
Oral route
200 mg - 3 tablets

Mifepristone
NDA No. 20-687

GENERIC DRUG ENFORCEMENT ACT OF 1992
CERTIFICATION STATEMENT

The Population Council hereby certifies that it did not and will not knowingly use in any capacity the services of any person debarred under subsections (a) or (b) of section 306 of the Federal Food, Drug, and Cosmetic Act in connection with NDA 20-687 for Mifepristone.

Signed: Ann Robbins

Ann Robbins, Ph.D.
Scientist
The Population Council

Date: 15 August 1996

APPEARS THIS WAY
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1 2/12/91

DRUG STUDIES IN PEDIATRIC PATIENTS
(To be completed for all NME's recommended for approval)

NDA # 20-687 Trade (generic) names mifepristone

Check any of the following that apply and explain, as necessary, on the next page:

___ 1. A proposed claim in the draft labeling is directed toward a specific pediatric illness. The application contains adequate and well-controlled studies in pediatric patients to support that claim.

___ 2. The draft labeling includes pediatric dosing information that is not based on adequate and well-controlled studies in children. The application contains a request under 21 CFR 210.58 or 314.126(c) for waiver of the requirement at 21 CFR 201.57(f) for A&WC studies in children.

___ a. The application contains data showing that the course of the disease and the effects of the drug are sufficiently similar in adults and children to permit extrapolation of the data from adults to children. The waiver request should be granted and a statement to that effect is included in the action letter.

___ b. The information included in the application does not adequately support the waiver request. The request should not be granted and a statement to that effect is included in the action letter. (Complete #3 or #4 below as appropriate.)

___ 3. Pediatric studies (e.g., dose-finding, pharmacokinetic, adverse reaction, adequate and well-controlled for safety and efficacy) should be done after approval. The drug product has some potential for use in children, but there is no reason to expect early widespread pediatric use (because, for example, alternative drugs are available or the condition is uncommon in children).

___ a. The applicant has committed to doing such studies as will be required.

___ (1) Studies are ongoing.
___ (2) Protocols have been submitted and approved.
___ (3) Protocols have been submitted and are under review.
___ (4) If no protocol has been submitted, on the next page explain the status of discussions.

___ b. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓ 4. Pediatric studies do not need to be encouraged because the drug product has little potential for use in children.

____ 5. If none of the above apply, explain.

Explain, as necessary, the foregoing items: _____

/S/

Signature of Preparer

8/12/76

Date

cc: Orig NDA
HFD-___/Div File
NDA Action Package

10/3/97

US Patent No.: 4,301,146

APPEARS THIS WAY
ON ORIGINAL

The Population Council

Center for
Medical Research

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New York, New York 10021
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Telex: 238274 POBI UR

To Whom It May Concern:

The undersigned declares that Patent No. 4,301,146 covers the formulation, composition, and/or method of use of Mifepristone [trade name undertermined]. This product is the subject of this application for which approval is being sought.

Signed on: October 3, 1995

for The Population Council

C. Wayne Bardin, MD

C. Wayne Bardin, M.D.
Vice President

APPEARS THIS WAY
ON ORIGINAL

United States Patent [19]
Sanvordeker

[11] 4,301,146
[45] Nov. 17, 1981

[54] STABILIZATION OF 16-OXYGENATED PROSTANOIC ACID DERIVATIVES

[75] Inventor: Dilip R. Sanvordeker, Elk Grove Village, Ill.

[73] Assignee: G. D. Searle & Co., Skokie, Ill.

[21] Appl. No.: 173,292

[22] Filed: Jul. 29, 1980

[51] Int. Cl.³ A61K 31/74; A61K 31/215; A61K 31/19

[52] U.S. Cl. 424/80; 424/305; 424/317; 424/362

[58] Field of Search 424/80, 78, 362, 305, 424/317

[56] References Cited

U.S. PATENT DOCUMENTS

3,826,823	7/1974	O'Rourke et al.	424/80
3,965,143	6/1976	Collins et al.	424/305
4,051,623	11/1977	Hoffmann et al.	424/80
4,127,647	11/1978	Sato et al.	424/78

Primary Examiner—Sam Rosen
Attorney, Agent, or Firm—Albert Tockman; W. Dennis Drehkoff

[57] ABSTRACT

A stable solid dosage form of the compound ±methyl(7-[3(α)-hydroxy-2-β-(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1α-yl]heptanoate, said solid dosage form comprising from about 50 to about 500 parts of a polymer selected from the group consisting of hydroxypropylmethyl cellulose and polyvinylpyrolidone per part of said compound.

22 Claims, No Drawings

APPEARS THIS WAY
ON ORIGINAL

STABILIZATION OF 16-OXYGENATED PROSTANOIC ACID DERIVATIVES

U.S. Pat. No. 3,965,143 discloses (±) methyl 7-[3(α)-hydroxy-2-β-(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1α-yl]heptanoate, a potent anti-secretory agent. A related anti-secretary agent, (+) methyl-7-[3(α)-hydroxy-2-β-(4-(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)oxycyclopent-1-yl]-1-hept-4-cis-enoate is disclosed in commonly assigned, copending U.S. Patent Application U.S. Ser. No. 06/098,290 filed Nov. 28, 1979.

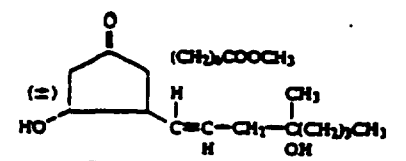
While the above compounds are potent anti-secretory agents, they are difficult to formulate because of their physical state as viscous liquids and their instability. The present invention provides stabilized compositions of the above anti-secretory agents.

The compounds are prostaglandin E-type compounds. Stabilization of prostaglandin E's is known in the art. See Derwent Abstract Nos. 90387A; 90386A; 90385A: 06805B and 32802W. Stabilization of the instant compounds has not previously been reported.

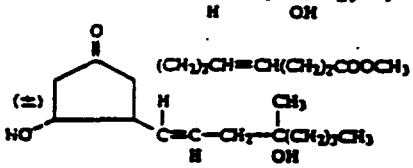
SUMMARY

The present invention provides improved compositions of two antisecretory agents: ±methyl(7-[3(α)-hydroxy-2-β-(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1α-yl]heptanoate(I) and ±methyl(7-[3(α)-hydroxy-2-β-(4-(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)oxycyclopent-1α-yl]-1-α-hept-4-cis-enoate(II). The compositions comprise a stabilized solid dispersion of a therapeutically effective amount of Compound I or II in a suitable polymer either alone or with fillers such as microcrystalline cellulose, mannitol and lactose.

The compounds are represented by Formulae I and II, respectively:



I



II

The compositions are generally prepared using a solvent stripping method.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The improved compositions of this invention are solid dosage forms of Compounds 1 and 2 comprising drug and hydroxypropylmethyl cellulose or polyvinyl-pyrrolidone in ratios of from about 50 to about 500 parts of said polymer per part of drug.

The solid dispersions of the present invention are prepared by: (1) dissolving the anti-secretory agent (Compound 1 or 2) in an appropriate volume of a suitable solvent; (2) dissolving a polymer selected from the group consisting of hydroxypropylmethyl cellulose or polyvinylpyrrolidone in an appropriate volume of a suitable solvent; (3) adding the drug solution to the polymer solution; (4) stirring for from about 1 to 5 hours, preferably for about 2 to 4 hours at room temperature; (5) adding, if desired, up to 1000 parts of a filler selected from the group consisting of microcrystalline cellulose, mannitol and lactose; (6) flash evaporating the solvent; (7) blow-drying the residue under a nitrogen atmosphere and thereafter drying the solid dispersion in vacuo, at temperatures of from about 30° to 60° C., preferably from about 2 to 4 hours; subsequently grinding and sieving the solid dispersion; and thereafter storing at temperatures of from about +5° C. to 30° C., preferably from about 7° C. to 25° C. prior to use.

The solid dispersions of the present invention can be filled in capsules with or without additional excipients, or can be compressed into tablets in the usual manner.

Suitable solvents for Compounds I and II include, but are not limited to ethanol 200 proof, ethanol 3A grade, ethanol U.S.P. and dichloromethane, A.R. grade. The preferred solvent is dichloromethane and ethanol 3A grade.

Suitable solvents for the polymer include ethanol 200 proof, ethanol 3A grade, ethanol U.S.P. and dichloromethane, A.R. grade. The preferred solvent is ethanol 3A grade.

The following examples further illustrate the present invention.

EXAMPLE 1

Preparation of Stabilized Solid Dispersion of (±) methyl 7-[3(α)-hydroxy-2-β-(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)oxocyclopent-1α-yl]heptanoate (Compound 1) and hydroxypropylmethyl cellulose (1:500 ratio)

Compound 1 (210 mg) was dissolved in 180 ml of dichloromethane and added to a solution of hydroxypropylmethyl cellulose (HPMC) (100 g) in 1000 ml of dichloromethane. The combined solutions were stirred for 1 hour at room temperature, after which the solvent was flash evaporated and the residue dried under nitrogen gas and then in vacuo for 2 hours at 35° C. The dispersion was then ground, sieved through a 40 mesh screen and stored.

EXAMPLE 2

Following the method of Example 1, a solid dispersion of Compound 1 and hydroxypropylmethyl cellulose in a 1:100 ratio was prepared from 1560 mg of Compound 1 and 150 g of hydroxypropylmethyl cellulose. Compound 1 was dissolved in 200 ml of absolute ethanol. Hydroxypropylmethyl cellulose was dissolved in 0.9 L of absolute ethanol. The two were mixed and processed as described earlier.

EXAMPLE 3

A solid dispersion of Compound 1 and hydroxypropylmethyl cellulose, 1:50 ratio to 1:150 was prepared from 100–200 mg of Compound 1 and 10–15 g of hydroxypropylmethyl cellulose, using dichloromethane.

EXAMPLE 4

A solid dispersion of Compound 1, hydroxypropylmethyl cellulose and mannitol 1:250: 749 was prepared following the method of Example 1 from 400 mg of Compound 1, 100 g of hydroxypropylmethyl cellulose and 299.6 g of mannitol, adding the mannitol after mix-

ing solution of Compound I in 100 ml and hydroxypropylmethyl cellulose in 2 liters of dichloromethane.

EXAMPLE 5

A solid dispersion containing 20 mg of Compound 1, 5 g of hydroxypropylmethyl cellulose and 14.98 g of Avicel PH101 microcrystalline cellulose (1:250: 749) was prepared by the method of Example 4, using dichloromethane (300 ml) as the solvent.

EXAMPLE 6

A solid dispersion containing 20 mg of Compound 1, 5 g of hydroxypropylmethyl cellulose and 14.98 g of mannitol (1:250: 749) was prepared by the method of Example 4 using dichloromethane as the solvent.

EXAMPLE 7

The stability the solid dispersions of Example 1, 2 and 3 was determined at 5° C., 40° C. over a 12-26 week period by incubating samples. The results are summarized in Table I (Example 1), Table II (Example 2) and Table III (Example 3) for a predetermined period at each temperature and thereafter assaying the samples by high pressure liquid chromatography for Compound 1. All analysis was done using a Waters Associate Liquid Chromatograph equipped with Model 6000A Pump, V6K Injector and Model 450 Variable Wavelength Detector set at VV, 205 mm at 1.10AUFS and a chart speed of 1 cm 1 min. Analysis was achieved utilizing a Partisil 10/25 ODS 25 cm×4.6 mm ID column (Whatman, Incorporated), eluted with acetonitrile at a flow rate of 2.0 ml/minute.

TABLE 1

Stability Data on Compound 1 alone and in HPMC Dispersion

A. Compound 1 alone (Unstabilized)

Storage Period		% Potency (Extraction + HPLC Assay)* Time in Weeks 0	1	2	3	4	6	8	12	14
Storage Temperature	55° C.	—	72.7	44.0	26.6	17.5	—	—	—	—
	40° C.	—	—	—	—	57.0	—	35.0	41.55	
	30° C.	—	—	—	—	—	79.6	—	75.3	—
	5°-7° C. (2 wks)	94.8 -		—	—	—	—	—	93.1	86.1

B. Compound 1 HPMC Dispersion

Storage Period		% Potency (Extraction + HPLC Assay)* Time in Weeks 0	1	2	3	4	6	8	12	14
Storage Temperature	55° C.	—	90.9	89.9	89.1	94.7	88.5	92.8	—	—
	40° C.	—	—	—	—	97.0	—	92.6	83.1	88.3
	30° C.	—	—	—	—	—	87.7	—	89.9	87.2
	5°-7° C. (2 wks)	94.4 -		—	—	—	—	—	82.5	87.3

*Average of duplicate assays/point.

TABLE 2

A. Solid State Stability of Compound 1: HPMC (1:100) Dispersion Prepared with Ethanol and Dichloromethane

Condition	% SC-29333 Remaining Time (Weeks) 0	1	2	3	4	6	8	12	26
70° C.	100	91.92	89.47	86.70	90.07				
55° C.	100	—	94.74	93.26	97.32		95.80	92.80	
40° C.	100	—	—	94.92	—	92.70	—	97.00	102.9
30° C.	100	—	—	—	99.63		91.41	98.52	104.7
5° C.	100	—	—	—			102.21	100.46	107.4

B. Solid Stability of Compound 1: HPMC (1:100) Dispersion Prepared with Methylene Chloride

Condition	% SC-29333 Remaining Time (Weeks) 0	1	2	3	4	6	8	12	36
70° C.	100	97.27	85.36	—	87.74				
55° C.	100	—	97.28	—	—	93.43	—	90.47	
30° C.	100	—	—	—	—	—	106.08	—	103.6
+5° C.	—	—	—	—	—	—	96.0	102.53	105.1

TABLE III

Solid State Stability of Compound 1: HPMC Dispersions (Comparison of Compound 1: HPMC Ratios 1:50, 1:100, 1:150)
% Compound 1 Remaining (Initial Assay as 100%)

	CONDITION											
	70° C. RATIO			55° C. RATIO			30° C. RATIO			+5° C. RATIO		
TIME (Weeks)	1:50	1:100	1:150	1:50	1:100	1:150	1:50	1:100	1:150	1:50	1:100	1:150
1	103.40	87.25	92.50	—	—	—	—	—	—	—	—	—
2	85.97	85.36	80.48	98.52	97.28	97.28	—	—	—	—	—	—
4	90.86	87.74	72.79	—	—	—	112.35	108.56	103.2	—	—	—
6				96.36	93.43	92.45	—	—	—	—	—	—
8				97.84	—	91.49	106.25	106.08	100	107.68	98.0	94.50
12				98.69	90.47	81.77				108.03	102.53	103.13

EXAMPLE 8

The stability of the solid dispersions of Example 4, 5 and 6 were determined under various conditions. The results (% of Compound 1 extracted) are set forth in TABLE IV.

TABLE IV

Effect of Excipients on Stability of Compound 1: HPMC Solid Dispersions

Example No.	Temperature	Period	% Compound 1 Extracted (HPLC Assay)
1	R.T.	initial	94.8 (100%)
	40° C.	18 weeks	90.17 (96.16%)
4	R.T.	initial	11.15 (100%)
	55° C.	4 weeks	110.5 (100%)
	55° C.	4 weeks	106.1 (95.45%)
5	R.T.	initial	110.7 (100%)
	55° C.	4 weeks	109.3 (101.2%)
	55° C.	8 weeks	112.3 (101.4%)
6	R.T.	initial	104.1 (100%)
	55° C.	2 weeks	91.8 (88.18%)
	55° C.	6 weeks	98.5 (94.62%)
	55° C.	8 weeks	95.7 (91.93%)
	55° C.	12 weeks	88.6 (85.11%)
	55° C.	17 weeks	84.9 (81.55%)
	70° C.	1 week	105.3 (101.1%)
	70° C.	2 weeks	94.6 (90.8%)
	70° C.	3 weeks	85.35 (82.18%)
	70° C.	4 weeks	73.10 (70.22%)
	70° C.	6 weeks	76.65 (73.63%)

EXAMPLE 9

Preparation of Filled Capsules

1.5 Grams of a solid dispersion of ±methyl(7-[3(α)-hydroxy-2-β-(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxocyclopent-1α-yl]heptanoate and polyvinylpyrrolidone, containing 200 μg of drug per 100 mg of dispersion, were blended with 7.5 g of lactose (DTG.U.S.P. grade powder). The mixture was placed on a ball mill for 10 minutes. Thereafter, Number 2 gelatin capsules were filled with an average of about 296 mg of the blended mixture. Each capsule thus contained approximately 100 μg of drug.

EXAMPLE 10

Preparation of Filled Capsules

To 4.8 grams of a solid dispersion of ±methyl(7-[3(α)-hydroxy-2β-4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)oxycyclopent-1-yl]-1-hept-4-cis-enoate and hydroxypropylmetiryl cellulose, containing 200 μg of drug per 100 mg of dispersion, was added 24.8 g of anhydrous DTG lactose. The powders were mixed intimately for 10 minutes with a mortor and pestle, and sifted three times through a 30 mesh screen. Thereafter, No. 2 gelatin capsules were filled with 314 mg of the blended mixture. Each capsule contained 106.9 μg of drug.

EXAMPLE 11

Preparation of Tablets

25,000 Tablets each containing 200 mcg of ±methyl (7-[3(α)-hydroxy-2-β-(4RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1-yl]heptanoate were prepared using a 1:100 solid dispersion of drug and hydroxy propyl methyl cellulose with the following ingredients:

Ingredient	Amount per batch(g)	Amount per dose (mg)
Solid Dispersion	511.75	20.47
Microcrystalline cellulose, N.F. (Avicel PH103, FMC Corp)	4388.25	175.53
Sodium glycolate starch, U.S.P.	75.0	3.0
Hydrogenated castor oil	25.0	1.0
	5000.00 mg	5,000.00 g

Tablets of varying dosages of drug can be prepared so long as the dosage per tablet or per dose administered is within the range of from about 50 to about 200 mcg per dose.

I claim:

1. A stable solid dispersion of the compound ±methyl(7-[3(α)-hydroxy-2-β-(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)-oxycyclopent-1α-yl]heptanoate, said solid dispersion comprising from about 50 to about 500 parts of a polymer selected from the group consisting of hydroxypropylmethyl cellulose and polyvinylpyrrolidone per part of said compound.

2. A dispersion of claim 1 additionally comprising a filler selected from the group consisting of microcrystalline cellulose, mannitol and lactose.

3. A dispersion of claim 2 wherein up to 1000 parts of filler per part of drug is employed.

4. A solid dispersion of claim 1 wherein said polymer is hydroxypropylmethyl cellulose.

5. A solid dispersion of claim 2 or 4 wherein said polymer is aydroxypropylmethyl cellulose and said filler is microcrystalline cellulose.

6. a solid dispersion of claim 2 or 4 wherein said polymer is hydroxypropylmethyl cellulose and said filler is mannitol.

7. A solid dosage form of claim 1 or 2 wherein said polymer is polyvinylpyrrolidone.

8. A solid dispersion of claim 2 or 4 wherein said polymer is polyvinylpropylene and said filler is microcrystalline cellulose.

9. A solid dispersion of claim 2 or 4 wherein said polymer is polyvinylpyrrolidone and said filler is mannitol.

10. A stable solid dosage form of the compound ±methyl-(7-[3(α)-hydroxy-2β-(4(RS)-4-hydroxy-4-methyl-trans-1-octen-1-yl)oxycyclopent-1α-yl]hept-4-cis-enoate, said solid dosage form comprising from about 50 to about 500 parts of a polymer selected from the group consisting of hydroxypropylmethyl cellulose and polyvinylpyrrolidone per part of said compound.

11. A dosage form of claim 10 additionally comprising a filler selected from the group consisting of microcrystalline cellulose, mannitol and lactose.

12. A dosage form of claim 11 wherein up to 1000 parts of filler per part of drug is employed.

13. A solid dosage form of claim 10 wherein said polymer is hydroxypropylmethyl cellulose.

14. A solid dosage form of claim 11 or 13 wherein said polymer is hydroxypropylmethyl cellulose and said filler is microcrystalline cellulose.

15. A solid dosage form of claim 11 or 13 wherein said polymer is hydroxypropylmethyl cellulose and said filler is mannitol.

16. A solid dosage form of claim 10 or 11 wherein said polymer is polyvinylpyrrolidone.

17. A solid dosage form of claim 11 or 13 or wherein said polymer is polyvinylpyrrolidone and said filler is microcrystalline cellulose.

18. A solid dosage form of claim 11 or 13 wherein said polymer is polyvinylpyrrolidone and said filler is mannitol.

19. A solid dosage form of claim 11 or 13 wherein said polymer is polyvinylpyrrolidone and said filler is lactose.

20. A solid dosage form of claim 11 or 13 wherein said polymer is hydroxypropylmethyl cellulose and said filler is lactose.

21. A solid dosage form of claim 2 or 4 wherein said polymer is hydroxypropylmethyl cellulose and said filler is lactose.

22. A solid dosage form of claim 2 or 4 wherein said polymer is polyvinylpyrrolidine and said filler is lactose.

* * * * *

APPEARS THIS WAY
ON ORIGINAL

US Patent No.: 4,386,085

The Population Council

Center for
Biomedical Research

1230 York Avenue
New York, New York 10021
Cable: Popblomed, New York
Facsimile: (212) 327-7678
Telephone: (212) 327-8731
Telex: 238274 POBI UR

To Whom It May Concern:

The undersigned declares that Patent No. 4,386,085 covers the formulation, composition, and/or method of useof Mifepristone [trade name undertermined]. This product is the subject of this application for which approval is being sought.

Signed on: October 3, 1995

for The Population Council

C. Wayne Bardin, MD

C. Wayne Bardin, M.D.
Vice President

APPEARS THIS WAY
ON ORIGINAL

United States Patent [19]
Teutsch et al.

[11] 4,386,085
[45] May 31, 1983

[54] NOVEL STEROIDS

[75] Inventors: Jean G. Teutsch, Pantin; Germain Costerousse, Saint-Maurice; Daniel Philibert, La Varenne Saint Hilaire; Roger Deraedt, Pavillons sous Bois, all of France

[73] Assignee: Roussel Uclaf, Paris, France

[21] Appl. No.: 338,077

[22] Filed: Jan. 8, 1982

[30] Foreign Application Priority Data

Jan. 9, 1981 [FR] France 81 00272

[51] Int. Cl.³ A01N 45/00; A61K 31/56

[52] U.S. Cl. ..... 424/238; 424/241; 424/243; 260/239.55 R; 260/239.55 C; 260/239.5; 260/397.45; 260/239.5; 260/397.1

[58] Field of Search ..... 424/238; 260/239.55 R, 260/397.45, 239.55 C, 239.5

[56] References Cited

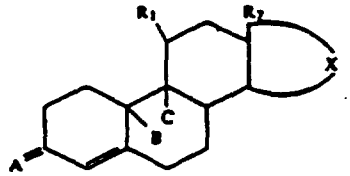
U.S. PATENT DOCUMENTS

4,147,695 4/1979 Teutsch ..... 260/239.55 R
4,233,296 11/1980 Teutsch et al. ..... 260/239.55 R

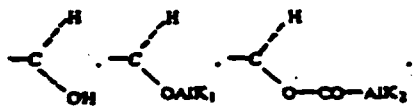
Primary Examiner—Elbert L. Roberts
Attorney, Agent, or Firm—Hammond & Littell, Weissenberger and Muserlian

[57] ABSTRACT

Novel 19-nor steroids and 19-nor-D-homo-steroids of the formula



wherein R_1 is an organic radical of 1 to 18 carbon atoms containing at least one atom selected from the group consisting of nitrogen, phosphorous and silicon with the atom immediately adjacent to the 11-carbon atom being carbon, R_2 is a hydrocarbon of 1 to 8 carbon atoms, X is selected from the group consisting of a pentagonal ring and a hexagonal ring optionally substituted and optionally containing a double bond, B and C together form a double bond or an epoxy group, the C=A group at position 3 is selected from the group consisting of C=O, ketal,



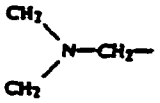
—C=NOH, —C=NOAlK$_3$ and =CH$_2$, AlK$_1$, AlK$_2$ and AlK$_3$ are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and their non-toxic, pharmaceutically acceptable acid addition salts having anti-glucocorticoid activity and a process for their preparation.

46 Claims, No Drawings

NOVEL STEROIDS

STATE OF THE ART

U.S. Pat. No. 4,233,296 describes steroids being substituted in the 11-position with substituents other than the present formula which require an organic substituent containing a nitrogen, phosphorous or silicon atom. U.S. Pat. No. 3,190,796 describes steroids having in a hydroxyl in the 11β-position. Schonemann et al [European Journal of Medicinal Chemistry, Chimica Therapeutica, Vol. 15, No. 4, (July, Aug. 1980), p. 333-335] describes steroids substituted in the 11β-position with CH_2=, $-CH_2OH$ and



OBJECTS OF THE INVENTION

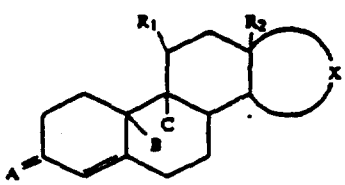
It is an object of the invention to provide the novel steroids of formula I and their non-toxic, pharmaceutically acceptable acid addition salts and a novel process and novel intermediates for their preparation.

It is another object of the invention to provide novel antiglucocorticoid compositions and to a novel method of inducing antiglucocorticoidal activity in warm-blooded animals.

These and other objects and advantages of the invention will become obvious from the following detailed description.

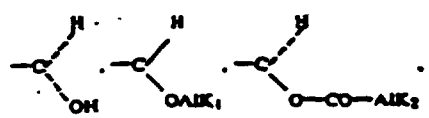
THE INVENTION

The novel steroids of the invention are selected from the group consisting of 19-nor steroids and 19-nor-D-homosteroids of the formula



I'

wherein R_1 is an organic radical of 1 to 18 carbon atoms containing at least one atom selected from the group consisting of nitrogen, phosphorous and silicon with the atom immediately adjacent to the 11-carbon atom being carbon, R_2 is a hydrocarbon of 1 to 8 carbon atoms, X is selected from the group consisting of a pentagonal ring and a hexagonal ring optionally substituted and optionally containing a double bond, B and C together form a double bond or an epoxy group, the C=A group at position 3 is selected from the group consisting of C=O, ketal,



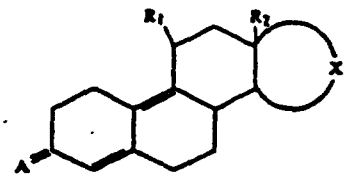
$-C=NOH$, $-C=NOAlK_3$ and $=CH_2$, AlK_1, AlK_2 and AlK_3 are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon

atoms and their non-toxic, pharmaceutically acceptable acid addition salts.

Preferably R_2 is a saturated alkyl of 1 to 4 carbon atoms such as methyl, ethyl, n-propyl or butyl and AlK_1, AlK_2 and AlK_3 are preferably methyl, ethyl, n-propyl, isopropyl or benzyl. X is preferably an optionally substituted remainder of a pentagonal ring.

Examples of suitable acids for the non-toxic, pharmaceutically acceptable acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid and organic acids such as acetic acid, formic acid, propionic acid, benzoic acid, maleic acid, fumaric acid, succinic acid, tartaric acid, citric acid, oxalic acid, glyoxylic acid, aspartic acid, alkane sulfonic acids such as methane sulfonic acid and ethane sulfonic acid, aryl sulfonic acids such as benzene sulfonic acid and p-toluene sulfonic acid and arylcarboxylic acid.

A preferred group of compounds are those of the formula



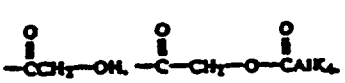
I

wherein R_1, R_2, A and X have the above definitions and their non-toxic, pharmaceutically acceptable acid addition salts.

Preferred compounds of formula I' are those wherein R_2 is methyl, those wherein X is the remainder of the pentagonal ring

wherein R_2 has the above definition, the dotted line in the 16,17-position is an optional double bond, Y is the group

a is 1 or 2, R_5 is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms, alkenyl and alkynyl of 2 to 8 carbon atoms, aryl of 6 to 14 carbon atoms and aralkyl of 7 to 15 carbon atoms, R_6 may be the same as R_5 and may be selected from the same group of members as R_5 or —OH, R_3 and R_4 are individually selected from the group consisting of hydrogen, —OH, $-OAlK_4$, $-OCOAlK_5$, alkenyl and alkynyl of 2 to 8 carbon atoms,



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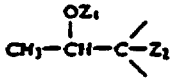
and —CN wherein AlK_4, AlK_5 and AlK_8 are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms. AlK_6 is selected from the group consisting of optionally substituted alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and AlK_7 is alkyl of 1 to 8 carbon atoms and R_3 and R_4 form the group



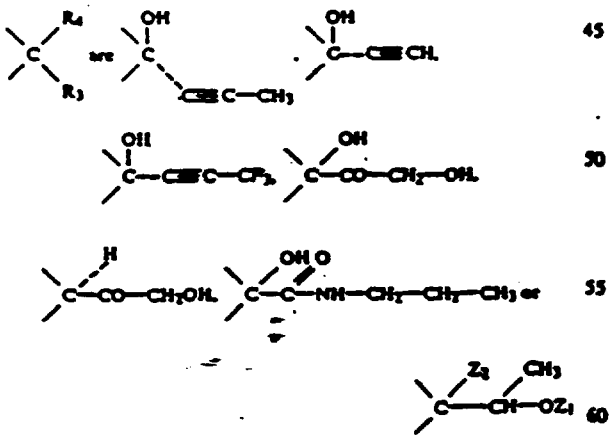
and Z_1 is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms and acyl of an organic carboxylic acid of 1 to 8 carbon atoms and Z_2 is alkyl of 1 to 8 carbon atoms and those where R_3 is different from R_6.

When R_5 or R_6 are alkyl, they are preferably methyl or ethyl and when they are alkenyl or alkynyl, they are vinyl, isopropenyl, allyl, ethynyl or propynyl. When R_5 and R_6 are aryl or aralkyl, they are phenyl or benzyl.

When R_3 or R_4 are $OAlK_4$ or

AlK_4 or AlK_5 are preferably methyl, ethyl, n-propyl, butyl, pentyl, hexyl or benzyl. When R_3 or R_4 are alkenyl or alkynyl, they are preferably vinyl, isopropenyl, allyl or 2-methylallyl or ethynyl or —C≡C-AlK_9 where AlK_9 is methyl, ethyl, propyl, isopropyl, isopropenyl, butyl, benzyl or CF_3—, AlK_6, AlK_7 or AlK_8 have preferably the same values as AlK_4 and AlK_5. The groups R_3 and R_4 are preferably different except where R_3 or R_4 each are hydrogen.

Among the preferred values of



wherein Z_1 is hydrogen, alkyl of 1 to 8 carbon atoms or acyl of a hydrocarbon of 2 to 8 carbon atoms such as acetyloxy or benzoyl and Z_2 is alkyl of 1 to 8 carbon atoms such as methyl.

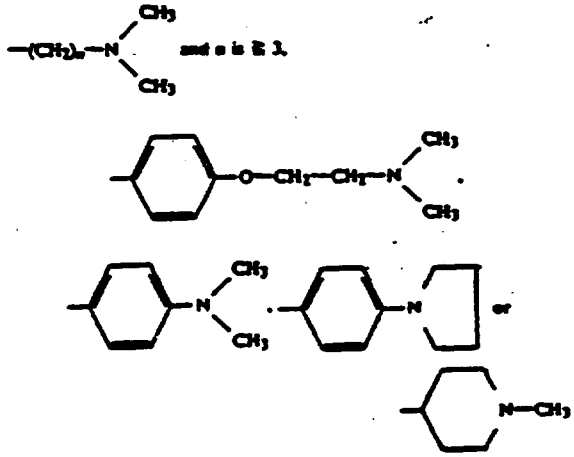
Other preferred compounds of formula I' are those wherein the D ring does not contain any ethylenic unsaturation. R_5 and R_6 are hydrogen, n is 1 and those compounds wherein =A is =O as well as those wherein R_1 is a hydrocarbon of 1 to 18 carbon atoms containing a nitrogen atom.

Especially preferred are the compounds of formula I' wherein R_1 is a primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of oxygen, nitrogen and sulfur at least one of which is nitrogen or is substituted with a nitrogen heterocycle. Examples of alkyl are methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, hexyl and cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Examples of heterocycle containing a nitrogen atom are 3-pyridyl, 4-pyridyl, 2-pyridyl, thiazolyl and piperidinyl.

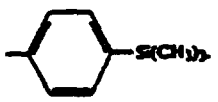
Equally preferred are compounds of formula I' wherein R_1 is a heterocycle containing at least one nitrogen atom optionally substituted with alkyl of 1 to 8 carbon atoms.

Other preferred compounds of formula I' are those wherein R_1 is aryl or aralkyl substituted with a group

wherein R_7 and R_8 are alkyl of 1 to 8 carbon atoms or primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatoms of the group consisting of nitrogen, sulfur or oxygen of which at least one is nitrogen or a heterocycle containing at least one nitrogen atom. Examples of alkyl are those mentioned above as preferred and aryl or aralkyl are preferably phenyl or benzyl and the preferred heterocycles are those mentioned above. Especially preferred are those wherein R_1 is 2-pyridyl, 3-pyridyl, 4-pyridyl.



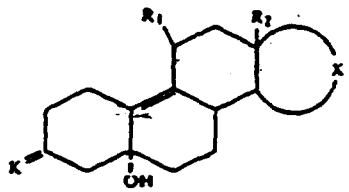
and especially those wherein R_1 is



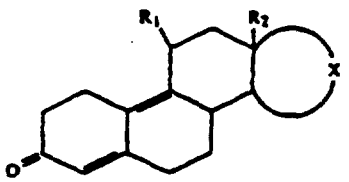
Among other preferred compounds are those wherein R_1 is a nitrogen oxide as well as those wherein

B and C form an epoxy. Especially preferred compounds are those of Examples 1, 3, 4, 8, 10, 11, 12, 14, 16, 17, 20, 22, 28 and 29.

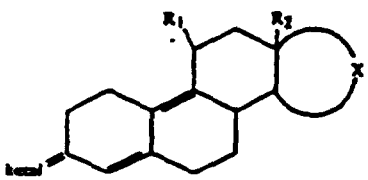
The novel process of the invention for the preparation of compounds of formula I' comprises reacting a compound of the formula



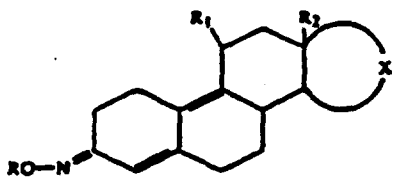
wherein K is a ketone blocked in the form of a ketal, thioketal, oxime or methyloxime and R_1, R_2 and X have the above definitions with a dehydration agent capable of freeing the ketone group to form a compound of the formula



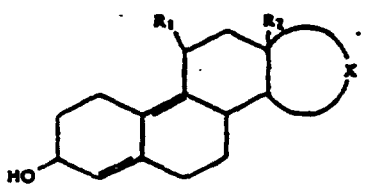
and either reacting the latter with a ketalization agent to obtain a compound of the formula



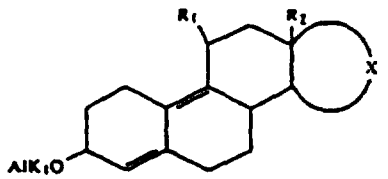
or reacting the compound of formula I_A' with NH_2OH or NH_2OAlK_3 wherein AlK_3 has the above definition to obtain a compound of the formula



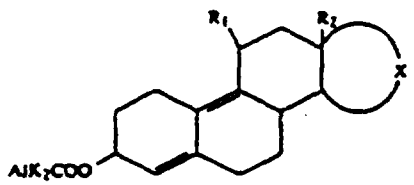
wherein R is hydrogen or AlK_3 or reacting a compound of formula I_A' with a reducing agent capable of selectively reducing the 3-keto group to obtain a compound of the formula



and reacting the latter with an etherification agent capable of introducing AlK_1 to obtain a compound of the formula

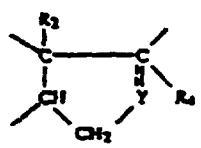


or reacting the compound of formula I_D' with an esterification agent capable of introducing $COAlK_2$ to obtain a compound of the formula



or transforming the compound of formula I_A' by known methods to a compound wherein C=A is CH_2 and reacting a compound of formula I_A', I_B', I_C', I_D', I_E' or I_F' with an acid to form the corresponding acid addition salt or with an oxidation agent to obtain when R_1 is a radical containing a nitrogen atom a compound having in the 11β-position a radical wherein the nitrogen atom is in the oxide form and B and C optionally form an epoxide bridge or when R_1 does not contain a nitrogen atom, a compound where B and C form an epoxide bridge and when the compound contains the nitrogen oxide and the B and C group form an epoxide bridge, selectively reducing the oxidized nitrogen atom in R_1 and optionally reacting the latter with an acid to form the acid addition salt.

The process of the invention is particularly useful for forming products of formula I' wherein X form a pentagonal ring of the formula



wherein R_2, R_3, R_4, Y and the dotted line in the 16,17-position have the above definition.

In a preferred mode of the process of the invention, the dehydration agent capable of freeing the ketone group is a sulfonic acid resin in the acid form such as a commercial sulfonic acid resin based on polystyrene or a styrene-divinylbenzene polymer but equally useful are inorganic acids such as sulfuric acid or hydrochloric acid in a lower alkanol or perchloric acid in acetic acid or a sulfonic acid such as p-toluene sulfonic acid.

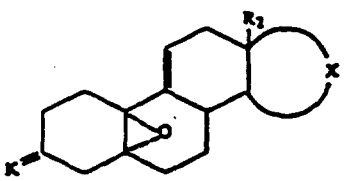
The ketalization agent is preferably an alcohol or a dialcohol in the presence of an organic acid such as oxalic acid or p-toluene sulfonic acid. The agent for reducing the ketone group is preferably an alkali metal hydride as discussed by Walkis [Chemical Society Review, Vol. 5, No. 1 (1976), p. 23]. The etherification agent is preferably an alkyl halide in the presence of a

base and the esterification agent is preferably a carboxylic acid derivative such as the acid anhydride or acid chloride in the presence of a base such as pyridine.

It goes without saying that when one of R_3 or R_4 in the compounds of formula I' obtained above is —OH, the compounds of formula I' may be reacted with an etherification agent or an esterification agent which is one of those discussed above. When R_3 or R_4 is a 17-acyloxy, the compound may be optionally saponified with a saponification agent such as a base like sodium hydroxide, potassium hydroxide, potassium amide or potassium tert.-butylate and the reaction is preferably effected in a lower alkanol such as ethanol or methanol but equally useful is lithium acetylide in ethylenediamine.

The oxidation agent is preferably a peracid such as m-chloroperbenzoic acid, peracetic acid or perphthalic acid or hydrogen peroxide alone or in the presence of hexachloroacetone or hexafluoroacetone. When it is desired to obtain a compound in which the nitrogen atom of R_1 is oxidized, one uses an equivalent of the oxidation agent and when it is desired to obtain a compound in which B and C form an epoxide bridge, two equivalents of agent are used. The selective reducing agent for the N-oxide is preferably triphenylphosphine and operating for example with acetic acid.

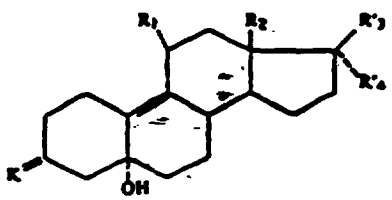
Another object of the invention is a process for the preparation of the compounds of formula II wherein a compound of the formula



III

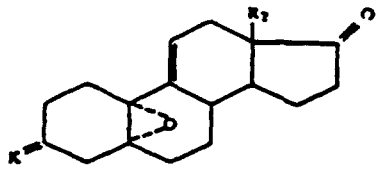
is reacted with a compound selected from the group consisting of $LiCu(R_1)_2$, LiR_1 and R_1Mg Hal wherein R_1 has the above definition and Hal is halogen in the presence of a cuprous halide. In a preferred mode of the said process, the reaction is effected at room temperature and the reactant is R_1Mg Hal in the presence of a cuprous salt.

Another object of the invention is a process for the preparation of a compound of the formula



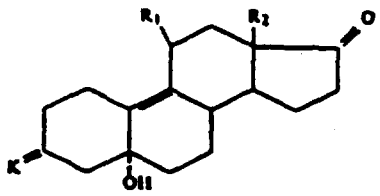
II'

wherein R_1, R_2 and K have the above definitions, R_3' is selected from the group consisting of —OH and OR_c, R_c is the residue AlK_4 of an ether group or $COAlK_3$ of an ester group and R_4' is hydrogen or alkenyl or alkynyl of 2 to 8 carbon atoms comprising reacting a compound of the formula



IV

with a compound selected from the group consisting of $LiCu(R_1)_2$, R_1Li and R_1Mg Hal in the presence of a cuprous halide to obtain a compound of the formula



V

and either reducing the latter to obtain the corresponding 17-ol compound or with an appropriate magnesium to obtain the corresponding 17α-substituted-17β-ol steroid or with an organometallic derivative such as a lithium or potassium derivative to obtain the corresponding 17α-substituted-17β-ol steroid or with a cyanuration agent to obtain the corresponding 17α-ol-17β-cyano steroid, protecting the hydroxy group and reacting the latter with an organometallic compound as discussed above to obtain the corresponding 17α-substituted-17β-ol steroid and in the case of one of the compounds obtained is 17-hydroxylated, reacting it with an etherification agent or esterification agent and in the case when one of the compounds contains a 17 substituent with a triple bond, reacting the latter with a reducing agent to obtain the corresponding ethylenic derivative.

In a preferred mode of the latter process, the reaction of the compound of formula IV with a compound of the group consisting of R_1Li, $LiCu(R_1)_2$ or R_1Mg Hal is effected under the previously described conditions. The different reactants for reaction with the compounds of formula V are known in steroid chemistry and are illustrated in the specific examples.

The novel intermediates of the invention are the compounds of formula II and V. Particularly preferred compounds of the invention are 3,3-[1,2-ethanediyl bisoxy]-11β-[4-trimethylsilyl-phenyl]-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-(4-pyridyl)-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N,-dimethylaminoethoxy)phenyl]-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17Δ-Δ^9-pregnene-20-yne-5α,17β-diol and 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-Δ^9-estrene-5α,17β-diol.

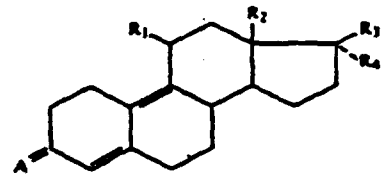
The compounds of formula III are especially of formula IV used to prepare the compounds of formula II or V are generally known compounds which can be prepared by reacting the corresponding $\Delta^{5(10),9(11)}$ steroids with an epoxidation agent selective for the 5(10)

double bond, for example with hydrogen peroxide in the presence of hexachloroacetone or hexafluoroacetone as described in French Pat. No. 2,423,486. The new compound, 3,3-[1,2-ethanediyl-bisoxy]-17α-(prop-1-ynyl)-5α,10α-epoxy-$\Delta^{9(11)}$-estrene-17β-ol is prepared in the Examples

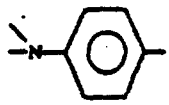
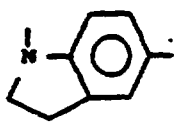
The starting compounds of formula II are described in lines 11 to 21 of column 4 of U.S. Pat. No. 4,147,695.

The following compounds are compounds falling within the scope of the invention:

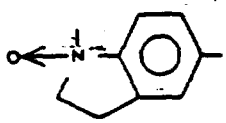
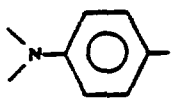
(A) compounds of the formula



wherein the A, R_1, R_2, R_3 and R_4 substitutes are indicated in Table I.

A	R_1	R_2	R_3	R_4
O		CH_3	OH	—C≡C—H
"	"	"	"	—C≡C—CF_3
"	"	"	"	—C≡C—CH_2CH_3
"	"	"	"	—CH_2—C≡C—H
"	"	"	"	—C≡C—$SiMe_3$
"	"	"	—C≡C—H	OH
"	"	"	—C≡C—$SiMe_3$	"
"	"	CH_2CH_3	OH	—C≡C—H
"	"	"	OH	—C≡C—CH_3
"	"	"	OH	—CH_2—C≡C—H
"	"	CH_3	—C(=O)—CH_2OH	H
"	"	"	"	OH
HO—N=(E)	"	"	OH	—C≡C—H
"	"	"	"	—C≡C—CH_3
"	"	"	—C≡C—H	OH
"	"	"	OH	—CH_2—C≡C—H
HO—N=(Z)	"	"	"	—C≡C—H
"	"	"	"	—C≡C—CH_3
"	"	"	"	—CH_2—C≡C—H
"	"	"	—C≡C—H	OH
O		"	OH	—C≡C—H
"	"	"	"	—C≡C—CF_3
"	"	"	"	—CH_2—C≡C—H
"	"	"	"	—C≡C—CH_2CH_3
"	"	"	"	—C≡C—Cl
"	"	"	"	—C≡C—$SiMe_3$
"	"	"	—C≡C—H	OH
"	"	"	—C≡C—$SiMe_3$	"
"	"	CH_2CH_3	OH	—C≡C—H
"	"	"	"	—C≡C—CH_3
"	"	"	"	—CH_2—C≡C—H
"	"	CH_3	—C(=O)—CH_2OH	—H
"	"	"	"	—OH
"	"	"	—C(=O)—CH_3	—H
HO—N=(E)	"	"	—OH	—C≡C—H
"	"	"	"	—C≡C—CH_3
"	"	"	"	—C≡C—CH_2CH_3
"	"	"	"	—CH_2—C≡C—H
"	"	"	—C≡C—H	—OH
"	"	"	—C(=O)—CH_2OH	H
HO—N=(Z)	"	"	"	"

-continued

A	R_1	R_2	R_3	R_4
-	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-CH_2Cl$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	-OH
O		-	-	-
-	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CF_3$
-	-	-	-	$-C\equiv C-Cl$
-	-	-	-	$-C\equiv C-CH_2Cl$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	-	$-C\equiv C-SiMe_3$
-	-	-	$-C(=O)-CH_2OH$	-H
HO—N=(E)	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	-OH
HO—N=(Z)	-	-	-	-
-	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
O		-	-	$-C\equiv C-CH_2CH_3$
-	-	-	-	$-C\equiv C-CF_3$
-	-	-	$-C\equiv C-SiMe_3$	-OH
-	-	-	$-C(=O)-CH_2OH$	-H
-	-	-	-	-OH
-	-	-	$-C(=O)-CH_3$	-H
-	-	CH_2CH_3	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-Cl$
-	-	-	-	$-C\equiv C-CH_2-CH_3$
-	-	-	-	$-C\equiv C-SiMe_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C(=O)-CH_2OH$	-H
HO—N=(E)	-	CH_3	$-C\equiv C-H$	-OH
-	-	-	$-C(=O)-CH_2OH$	-H
-	-	-	OH	$-CH_2-C\equiv C-H$
HO—N=(Z)	-	-	$-C\equiv C-H$	-OH
-	-	-	$-C(=O)-CH_2OH$	-H

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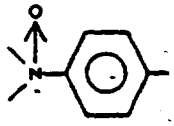
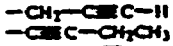
A	R_1	R_2	R_3	R_4
O		-	-	-
-	-	-		
-	-	-	OH	
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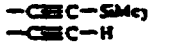
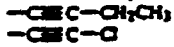
-	-	-	-	
HO—N=(E)	-	-	-	
-	-	-	-	
-	-	-	-	
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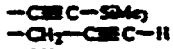
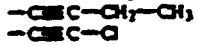
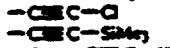
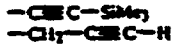
-	-	-	-	
-	-	-		
HO—N=(Z)	-	-	-	-
-	-	-	OH	
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-	-	
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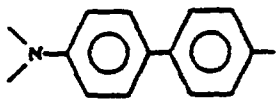
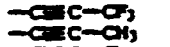
O		-	-	
-	-	-	-	
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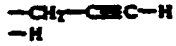
-	-	-	-	
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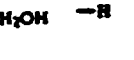
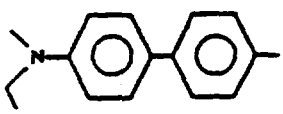
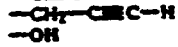
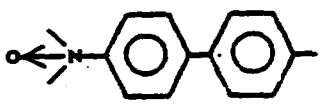
-	-	-		
-	-	-		
-		-	-	-
-	-	-	OH	
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-		
-		-	-	-
-	-	-	OH	
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-	-	
-		-	-	-
-	-	-	-	
-	-	-		
-	-	-		

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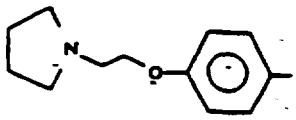
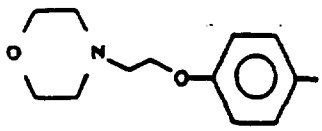
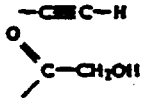
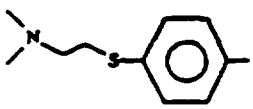
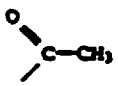
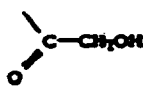
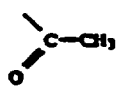
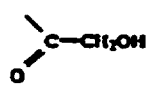
A	R_1	R_2	R_3	R_4
				
			$-C\equiv C-H$	$-OH$
			$-OH$	$-C\equiv C-H$
				$-C\equiv C-CH_3$
				$-CH_2-C\equiv C-H$
				$-C\equiv C-H$
				
				$-C\equiv C-CH_3$
				$-CH_2-C\equiv C-H$
			$-C\equiv C-H$	$-OH$
				$-H$
				
			$-C\equiv C-H$	OH
			OH	$-C\equiv C-CF_3$
				$-C\equiv C-H$
				$-CH_2-CH=CH_2$
				$CH_2-C\equiv C-H$
				$-CH_2$
				$-CH_3$
			OH	$-CH_2-CN$
HO—N=(E)				$-C\equiv C-H$
				$-C\equiv C-CH_3$
				$-C\equiv C-CH_2CH_3$
				$-C\equiv C-Cl$
				$-CH_2-C\equiv C-H$
			$-C\equiv C-H$	$-OH$
				$-H$
HO—N=(Z)				
			$-C\equiv C-H$	$-OH$
			OH	$-C\equiv C-H$
				$-C\equiv C-CH_3$
				$-C\equiv C-CH_2-CH_3$
				$-C\equiv C-Cl$
				$-CH_2-C\equiv C-H$
O		CH_2CH_3		$-C\equiv C-H$
				$-C\equiv C-CH_3$
				$-CH_2-C\equiv C-H$
				$-CH_2-CH=CH_2$
				$-CH_3$
				
				$-H$
				
			$-C\equiv C-H$	$-OH$

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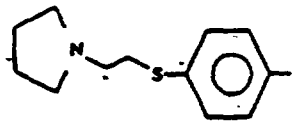
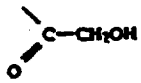
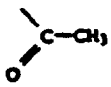
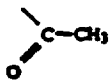
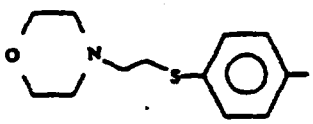
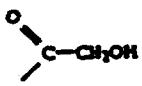
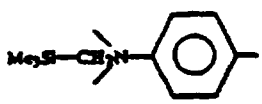
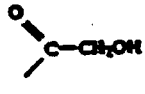
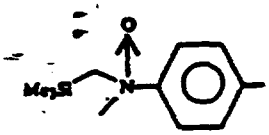
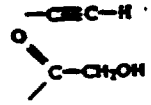
A	R_1	R_2	R_3	R_4
-		CH_3	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-Cl$
-	-	-	-	$-C\equiv C-CH_2CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	-	$-CH_2-CH=CH_2$
-	-	-	$-C\equiv C-H$	$-OH$
-	-	-		$-H$
-	-	-		
-	-	-		$-CH_3$
-	-	-		
-	-	-		$-H$
-	-	-		
-		-	-	-
-	-	-	-	$-CH_3$
-	-	-		$-H$
-	-	-		
-	-	-	$-C\equiv C-H$	$-OH$
-	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-Cl$
-	-	-	-	$-C\equiv C-CH_2CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	-	$-CH_2-CH=CH_2$
-	-	-	-	$-C\equiv C-H$
-				
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	$-OH$
-	-	-		$-H$
-	-	-		
-		-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	$-OH$
-	-	-		$-H$
-	-	-		

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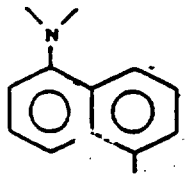
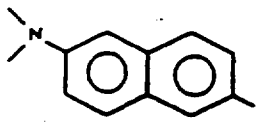
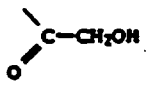
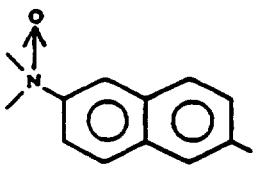
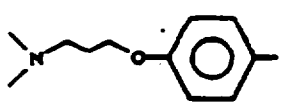
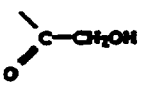
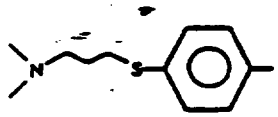
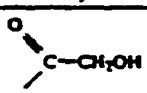
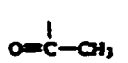
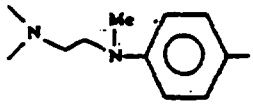
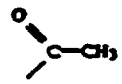
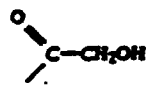
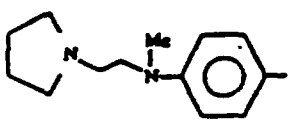
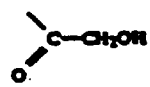
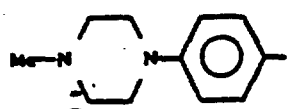
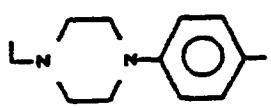
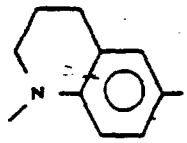
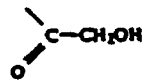
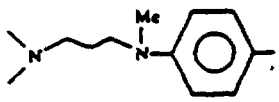
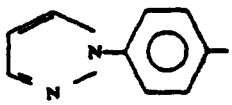
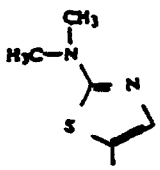
A	R_1	R_2	R_3	R_4
-		-	OH	$-C\equiv C-CH_3$
-		-	-	$-CH_2-C\equiv C-H$
-		-	-	$-C\equiv C-H$
-		-	-	$-C\equiv C-CH_3$
-		-	-	$-C\equiv C-Cl$
-		-	-	$-CH_2-C\equiv C-H$
-		-	$-C\equiv C-H$	-OH
-		-		-H
-		-		
-		-	-	-
-	-	-	$-C\equiv C-H$	-OH
-	-	-	-OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-Cl$
-	-	-	-	$-CH_2-C\equiv C-H$
-	Me_3SCH_2-	-	-	$-C\equiv C-H$
-		-	-	$-C\equiv C-CH_3$
-		-	-	$-CH_2-C\equiv C-H$
-		-	$-C\equiv C-H$	-OH
HO—N=(E)		-	-	-
-		-	OH	$-C\equiv C-H$
-		-	-	$-C\equiv C-CH_3$
-		-	-	$-CH_2-C\equiv C-H$
HO—N=(Z)		-	$-C\equiv C-H$	-OH
-		-	OH	$-C\equiv C-H$
-		-	-	$-C\equiv C-CH_3$
-		-	-	$-CH_2-C\equiv C-H$
O		-	-	$-C\equiv C-CH_3$
-	-	-		-H
-	-	-		
-		-	-	-
-	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	-	$-CH_2-CH=CH_2$
-	-	-	-	$-CH_2CN$
-	-	-	$-C\equiv C-H$	-OH

-continued

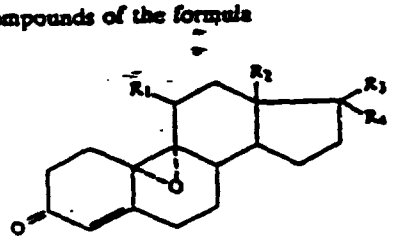
A	R_1	R_2	R_3	R_4
-	-	-		—H
-	-	-		—CH_3
-	-	-	OH	—H
-		-	-	—C≡C—H
-	-	-	-	—C≡C—CF_3
-	-	-	-	—C≡C—CH_2CH_3
-	-	-	-	—C≡C—Cl
-	-	-	-	—CH_2—C≡C—H
-	-	-	—C≡C—H	—OH
-	-	-		—H
-	-	-		—CH_3
-	-	CH_2CH_3	OH	—C≡C—H
-	-	-	-	—C≡C—CH_3
-	-	-	-	—CH_2—C≡C—H
-	-	-	—C≡C—H	—OH
-	-	-		—H
-		CH_3	OH	—C≡C—H
-	-	-	-	—C≡C—CH_3
-	-	-	-	—CH_2—C≡C—H
-	-	-	—C≡C—H	—OH
-	-	-		—H
-		-	-	-
-	-	-	—C≡C—H	—OH
-	-	-	OH	—C≡C—H
-	-	-	-	—CH_2—C≡C—H
-	-	-	-	—CH_2—CH=CH_2
-	-	-	-	—CH_2CN
-		-	-	—C≡C—H

25

-continued

A	R_1	R_2	R_3	R_4
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	-	$-CH_2-CH=CH_2$
-	-	-	-	$-CH_2-CN$
-	-	-	$-C\equiv C-H$	-OH
-		-	-OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	-OH
-	-	-		-H
-		-	-	-
-	-	-	$-C\equiv C-H$	OH
-	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	-	-H
-	-	-	-	$-CH_3$
-		-	-	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-CF_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	-OH
-		-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-CF_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	-OH
-	-	-	$-C\equiv C-CH_3$	-

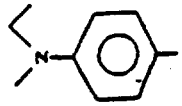
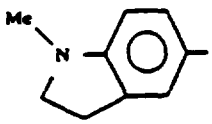
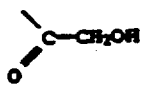
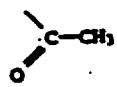
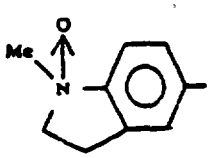
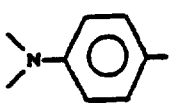
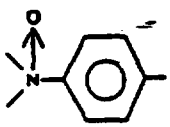
(B) compounds of the formula



(60)

wherein R_1, R_2, R_3 and R_4 have the definitions in Table II

(65)

R_1	R_2	R_3	R_4
	CH_3	OH	$-C\equiv C-H$
"	"	"	$-C\equiv C-CH_3$
"	"	"	$-C\equiv C-CF_3$
"	"	"	$-CH_2CH_3$
"	"	"	$-CH_2-C\equiv C-H$
"	"	$-C\equiv C-H$	$-OH$
"	"	OH	$-C\equiv C-H$
	"	"	$-C\equiv C-CH_3$
"	"	"	$-C\equiv C-CF_3$
"	"	"	$-C\equiv C-CH_2CH_3$
"	"	"	$-CH_2-C\equiv C-H$
"	"	"	$-H$
"	"	"	$-CH_2CH_3$
"	"	$-C\equiv C-H$	$-OH$
"	"		$-H$
			
"	"		$-CH_3$
			
	"	"	"
"	"	OH	$-C\equiv C-H$
"	"	"	$-C\equiv C-CH_3$
"	"	"	$-C\equiv C-CF_3$
"	"	"	$-CH_2CH_3$
"	"	"	$-CH_2-C\equiv C-H$
"	"	$-C\equiv C-H$	$-OH$
"	"	OH	H
	"	$-C(=O)-CH_3$	CH_3
"	"	OH	$-C\equiv C-H$
"	"	"	$-C\equiv C-CH_3$
"	"	"	$-C\equiv C-CF_3$
"	"	"	$-CH_2CH_3$
"	"	"	$-CH_2-C\equiv C-H$
	"	"	$-C\equiv C-H$
"	"	"	$-C\equiv C-CH_3$
"	"	"	$-C\equiv C-CF_3$
"	"	"	$-CH_2-CH_3$
"	"	"	$-CH_2-C\equiv C-H$
"	"	"	H
"	"	"	CH_3

-continued

R_1	R_2	R_3	R_4
-	-	$-C\equiv C-H$	OH

Also prepared are the epoxides of the compounds of Table II.

The antiglucocorticoid compositions of the invention are comprised of an antiglucocorticoidally effective amount of at least one compound of formula I' and its non-toxic-pharmaceutically acceptable acid addition salts and an inert pharmaceutical carrier or excipient. The compositions may be in the form of tablets, dragees, gelules, granules, suppositories, injectable solutions or suspensions, pomades cremes and gels.

Examples of suitable excipients are talc, arabic gum, lactose, starch, magnesium stearate, cacao butter, aqueous or non-aqueous vehicles, fatty bodies of animal or vegetable origin, paraffinic derivatives, glycols, diverse wetting agents, dispersants or emulsifiers and preservatives.

The compositions of the invention have remarkable antiglucocorticoid properties as can be seen from the pharmalogical data infra. The study of the products against hormonal receptors shows that the compositions possess progestomimetic activity or anti-progestomimetic, androgenic or antiandrogenic activity.

The compositions are used principally against secondary effects of glucocorticoids and are equally useful against troubles due to a hypersecretion of glucocorticoids and especially against aging in general and are particularly active against hypertension, atherosclerosis, osteoporosis, diabetes, obesity as well as depression of immunity and insomnia. The compositions of the invention also possess antiprogestomimetic activity and are useful for the preparation of original contraceptives and are equally useful against hormonal irregularities.

Some of the compounds of formula I' and their acid addition salts also possess progestomimetic activity and are useful for the treatment of amenorrhea, dysmenorrhea and luteal insufficiencies.

The compositions of the invention also present antiandrogenic activity making them useful for the treatment of hypertrophia, hyperandrogenia, anemia, hirsutism and acne.

The novel method of the invention of inducing antiglucocorticoid activity in warm-blooded animals, including humans, comprises administering to warm-blooded animals an antiglucocorticoidally effective amount of at least one compound of formula I' and their non-toxic, pharmaceutically acceptable acid addition salts. The usual daily dose is 0,15 to 15 mg/kg depending on the specific condition being treated and the compound used and the method of administration. The active compound may be administered orally, rectally, parenterally or locally.

In the following examples there are described several preferred embodiments to illustrate the invention. However, it is to be understood that the invention is not intended to be limited to the specific embodiments.

EXAMPLE 1

11β-(4-pyridyl)-17α-(prop-1-ynyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-17α-(prop-1-ynyl)-$\Delta^{5(10),\ 9(11)}$-estradiene-17β-ol

207 ml of a solution of 1.15% ethyl magnesium bromide in tetrahydrofuran were stirred at 0° C. while bubbling gaseous propyne dried over calcium chloride therethrough for 90 minutes and the temperature was then allowed to return to room temperature. The mixture was stirred for one hour while the bubbling was continued. Then a solution of 30 g of 3,3-[1,2-ethanediyl-bisoxy]-$\Delta^{5(10),\ 9(11)}$-estradiene-17-one in 120 ml of anhydrous tetrahydrofuran and one drop of triethylamine was added to the mixture over 30 minutes and the mixture was stirred for 2 hours at room temperature and was then poured into a mixture of ice, distilled water and ammonium chloride. The stirred mixture was extracted 3 times with ether and the organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The residue was dried under reduced pressure to obtain 35.25 g of 3,3-[1,2-ethanediyl-bisoxy]-17α-(prop-1-ynyl)-$\Delta^{5(10),\ 9(11)}$-estradiene-17β-ol.

NMR Spectrum (deuterochloroform): Peaks at 0.83 ppm (hydrogens of 18-methyl); at 1.85 ppm (hydrogens of methyl of C≡C—CH_3); at 5.65 ppm (hydrogens of 11-carbon); at 4 ppm (hydrogens of ethylene ketal).

STEP B: 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol

A mixture of 30 g of the product of Step A in 150 ml of methylene chloride was stirred while bubbling nitrogen therethrough and after cooling the mixture to 0° C., 1.8 ml of hexafluoroacetone sesquihydrate were added all at once. The mixture was stirred while 4.35 ml of 85% oxygenated water were added and the mixture was stirred at 0° C. for 72 hours while continuing to bubble nitrogen therethrough. The solution was poured into a mixture of 250 g of ice and 500 ml of 0.2 N sodium thiosulfate solution and the mixture was stirred for a few moments and was then extracted with methylene chloride. The organic phase was washed with distilled water, dried over sodium sulfate in the presence of pyridine and evaporated to dryness under reduced pressure. The residue was dried under reduced pressure and the 31.6 g of residue were chromatographed over silica gel. Elution with a 9-1 benzeneethyl acetate mixture yield 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol.

NMR Spectrum (deuterochloroform): Peaks at 0.82 ppm (hydrogens of 18-CH_3); at 1.83 ppm (hydrogens of methyl of C≡C—CH_3); at 6.1 ppm (hydrogens of 11-carbon); at 3.92 ppm (hydrogens of ethylene ketal).

STEP C: 3,3-[1,2-ethanediyl-bisoxy]-11β-(4-pyridyl)-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

100 ml of a tetrahydrofuran solution of 0.5 to 0.6 M 4-chloropyridyl magnesium bromide prepared from 15 g of 4-chloro-pyridine and 6 g of magnesium was added at 20° C. to a solution of 6.16 g of dimethyl sulfide-cuprous bromide complex in 40 ml of tetrahydrofuran and the mixture was stirred under an inert atmosphere at room temperature for 20 minutes. Then, a solution containing 3.7 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol was added thereto over 10 minutes and the mixture was stirred at room temperature for one hour and was then poured into a mixture of cold water and ammonium chloride. The mixture was stirred at room temperature for 30 minutes and was extracted with ether. The or-

ganic phase was washed with an aqueous saturated sodium chloride solution, was dried and evaporated to dryness under reduced pressure. The 6 g of residue were chromatographed over silica gel and eluted with a 1-1 methylene chloride-acetone mixture containing 1 ppm of triethylamine to obtain 3.15 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-(4-pyridyl)-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol which was dried towards 60° C. at 0.1 mm Hg which had a specific rotation of $[\alpha]_D^{20} = -52° \pm 1.5°$ (c=1% in chloroform).

STEP D: 11β-(4-pyridyl)-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A solution of 2.9 g of the product of Step C, 14 ml of methanol and 7 ml of 2 N hydrochloric acid was stirred under an inert atmosphere at room temperature for 3 hours and was then admixed with a solution of 200 ml of ether and 90 ml of aqueous saturated sodium bicarbonate solution. The mixture was stirred at room temperature for 15 minutes and the decanted aqueous phase was extracted with ether. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness under reduced pressure. The 2.3 g of residue were chromatographed over silica gel and eluted with a 6-4 methylene chloride-acetone mixture. The 1.7 g of product was dried for 24 hours at 0.1 mm Hg and for 8 hours at 80° C. to obtain 11β-(4-pyridyl)-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +30.5° \pm 1°$ (c=1% in chloroform).

Using the same procedure, 11β-(3-pyridyl)-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +14°$ (c=1% in chloroform) and 11β-(2-pyridyl)-17α-(prop-1-yny)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = -2°$ (c=1% in chloroform) were prepared.

EXAMPLE 2

11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A:
3,3-[1,2-ethanediyl-bisoxy]-11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

12.33 g of dimethyl sulfide-cuprous bromide complex were added over 5 minutes at 0° C. to a solution of 0.85 M of 3-(N,N-dimethylamino)-propyl magnesium chloride [prepared from 42 g of chloro 3-(N,N-dimethylamino)-propane and 10.5 g of magnesium] and the mixture was stirred at 0° C. for 25 minutes. A solution of 3.70 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol in 50 ml of tetrahydrofuran was added to the mixture dropwise and the mixture was then stirred at 0° C. for 3 hours and was poured into a mixture of 40 g of ammonium chloride and 200 ml of iced water. The mixture was stirred at room temperature for 15 minutes and was then extracted with ether. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness under reduced pressure. The 4.6 g of residue were chromatographed over silica gel and eluted with an 8-2 methylene chloride-methanol mixture to obtain 2.55 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol with a specific rotation of $[\alpha]_D^{20} = -86° \pm 1.5$ (c=1% in chloroform).

STEP B: 11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A mixture of 2.4 g of the product of Step A, 14 ml of methanol and 7 ml of 2 N hydrochloric acid was stirred under an inert atmosphere at room temperature for 4 hours and then 200 ml of isopropyl ether and 90 ml of aqueous saturated sodium bicarbonate solution were added thereto. The mixture was stirred at room temperature for 30 minutes and the decanted aqueous phase was extracted with ether. The organic extract was washed with aqueous saturated sodium chloride solution, was dried and evaporated to dryness under reduced pressure. The 1.8 g of residue were chromatographed over silica gel and eluted with an 8-2 chloroform-methanol mixture. The 1.30 g of product were dried at 30° to 40° C. at 0.1 mm Hg to obtain 1.25 g of 11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = -114° \pm 2.5°$ (c=1% in chloroform).

EXAMPLE 3

11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

A solution of 24 g of 4-(N,N-dimethylaminoethoxy)-bromobenzene was added dropwise over 45 minutes to 90 ml of anhydrous tetrahydrofuran and 2 ml of 1,2-dibromoethane were added as catalyst. After the addition, the mixture was stirred at 25° C. for one hour to obtain a solution of 0.7 M of 4-(N,N-dimethylaminoethoxy)-bromobenzene magnesium which was then added to a solution of 6.16 g of dimethylsulfide-cuprous bromide complex in 20 ml of tetrahydrofuran. The mixture was stirred at room temperature for 20 minutes and a solution of 3.7 g of 3,3-[1,2-(ethanediyl-bisoxy)]-5α,10α-epoxy-17α-prop-1-ynyl-$\Delta^{9(11)}$-estrene-17β-ol in 50 ml of tetrahydrofuran was added thereto dropwise over a few minutes. The mixture was stirred under an inert atmosphere for one hour and was then poured into a solution of 15 g of ammonium chloride in 20 ml of iced water. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, was dried and evaporated to dryness under reduced pressure. The 18.3 g of oil were chromatographed over silica gel and eluted with chloroform to obtain 4.5 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol with a specific rotation of $[\alpha]_D^{20} = -44° \pm 1.5°$ (c=1% in chloroform).

STEP B: 11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

9.5 ml of 2 N hydrochloric acid were added to a solution of 4.5 g of the product of Step A in 20 ml of methanol and the solution was stirred at room temperature for 2 hours. 260 ml of ether and 110 ml of an aqueous saturated sodium bicarbonate solution were added to the mixture which was stirred at room temperature for 15 minutes. The decanted aqueous phase was extracted with ether and the organic phase was dried and evaporated to dryness under reduced pressure. The 3.3 g of residue were chromatographed over silica gel and eluted with a 92.5-7.5 methylene chloride-methanol mixture to obtain 1.8 g of amorphous 11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +71°$ (c=1% in chloroform).

EXAMPLE 4

11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ9-estrene-5α,17β-diol

A solution of 38 mmoles of p-dimethylaminophenyl magnesium bromide in tetrahydrofuran was added to a suspension of 4.1 g of a cuprous bromide-dimethylsulfide complex in 20 ml of tetrahydrofuran and then a solution of 2.45 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-Δ9(11)-estrene-17β-ol in tetrahydrofuran was added thereto. The mixture was stirred for 10 minutes and was then hydrolyzed with 50 ml of aqueous saturated ammonium chloride solution. The decanted aqueous phase was extracted with ether and the organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The 11 g of residue were chromatographed over silica gel and eluted with a 6-4 cyclohexane-ethyl acetate mixture to obtain 1.8 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ9-estrene-5α,17β-diol which after crystallization from isopropyl ether and ethyl acetate had a specific rotation of $[\alpha]_D^{20} = -66.5°$ (c=1% in chloroform) and a melting point of 210° C. and 750 mg of the corresponding 11α-compound.

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one

2 ml of concentrated hydrochloric acid were added to a solution of 1.53 g of the product of Step A in 60 ml of methanol and after stirring the mixture for 30 minutes at room temperature, 150 ml of ether and then 50 ml of aqueous N sodium hydroxide solution were added thereto. The reaction mixture was stirred for 15 minutes and the decanted organic phase was dried and evaporated to dryness under reduced pressure. The 1.4 g of residue were chromatographed over silica gel and was eluted with a 7-3 cyclohexane-ethyl acetate mixture to obtain 0.932 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one melting at 150° C. and a specific rotation of $[\alpha]_D^{20} = +138.5°$ (c=0.5% in chloroform).

EXAMPLE 5

11β-[4-trimethylsilyl-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-(4-trimethylsilylphenyl)-17α-(prop-1-ynyl)-Δ9-estrene-5α,17β-diol

200 mg of cuprous chloride were added under an inert atmosphere at −30° C. to 45 ml of solution of 0.65 M of 4-trimethylsilyl-phenyl magnesium bromide in tetrahydrofuran and a solution of 3.3 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-Δ9(11)-estrene-17β-ol in 25 ml of tetrahydrofuran were added thereto dropwise at −20° C. After one hour, the mixture was hydrolyzed with aqueous ammonium chloride solution and was extracted with ether. The organic phase was dried and evaporated to dryness under reduced pressure and the residue was chromatographed over silica gel. Elution with a 94-6 methylene chloride-acetone mixture containing 0.1% of triethylamine yielded 2.087 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-(4-trimethylsilyl-phenyl)-17α-(prop-1-ynyl)-Δ9-estrene-5α,17β-diol which after crystallization from isopropyl ether and then ethyl acetate melted at 226° C. and a specific rotation of $[\alpha]_D^{20} = -60° \pm 1.5°$ (c=0.9% in chloroform).

STEP B: 11β-(4-trimethylsilyl-phenyl)-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one

1.7 g of Redex sulfonic acid resin were added to a solution of 1.68 g of the product of Step A in 17 ml of 90% alcol and the mixture was refluxed for 30 minutes and vacuum filtered. The filter was rinsed with methylene chloride and the filtrate was evaporated to dryness under reduced pressure. The residue was taken up in methylene chloride and the solution was dried and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel and was eluted with an 85-15 benzene-ethyl acetate mixture to obtain 1.217 g of 11β-(4-trimethylsilyl-phenyl)-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one melting at 212° C. and having a specific rotation of $[\alpha]_D^{20} = +94°$ (c=0.9% in chloroform).

The same procedure was used to prepare 11β-[3-trimethylsilyl-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +52.5 \pm 2°$ (c=1% in chloroform).

EXAMPLE 6

11β-[4-(N,N-dimethylamino)-phenyl]-17β-ethynyl-Δ4,9-estradiene-17α-ol-3-one

STEP A: 3,3-dimethoxy-17β-ethynyl-Δ5(10),9(11)-estradiene-17α-ol

A mixture of 16.8 g of 3,3-dimethoxy-17α-ethynyl-Δ5(10),9(11)-estradiene-17β-ol, 175 ml of anhydrous tetrahydrofuran and 4.35 g of lithium bromide was stirred at room temperature for 5 minutes and then the mixture was cooled to −60° C. and 3.9 ml of methane sulfonyl chloride were added thereto. The mixture was stirred at −60° C. for one hour and was then poured into 500 ml of aqueous saturated ammonium chloride solution. The mixture was stirred for 10 minutes and was extracted with methylene chloride. The organic phase was dried and after the addition of 2.5 ml of pyridine, the mixture was evaporated to dryness at 0° C. under reduced pressure. 75 ml of tetrahydrofuran were added to the residue and 12.5 ml of 0.75 g of silver nitrate in water were added thereto. The mixture was held at −30° C. for 18 hours and at room temperature for 4 hours and was then poured into 500 ml of aqueous semisaturated ammonium chloride solution containing 5 g of sodium cyanide. The mixture was stirred at 20° C. for 30 minutes and was extracted with chloroform. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel and was eluted with a 9-1 petroleum ether-ethyl acetate mixture to obtain 3 g of 3,3-dimethoxy-17β-ethynyl-Δ5(10),9(11)-estradiene-17α-ol melting at −150° C. and having a specific rotation of $[\alpha]_D^{20} = +125° \pm 2.5°$ (c=1% in chloroform).

STEP B: 3,3-dimethoxy-5α,10α-epoxy-17β-ethynyl-Δ9(11)-estrene-17α-ol

0.12 ml of hexachloroacetone and 0.65 ml of oxygenated water (200 volumes) were added at 0° C. to a mixture of 2.6 g of the product of Step A, 12 ml of methylene chloride and one drop of pyridine and the mixture was stirred for one hour after which 13 ml of chloroform were added. The mixture was stirred for 18 hours and was then poured into 100 ml of aqueous saturated sodium thiosulfate solution. The mixture was stirred for

10 minutes and was extracted with chloroform. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness under reduced pressure to obtain 2.8 g of 3,3-dimethoxy-5α,10α-epoxy-17β-ethynyl-$\Delta^{9(11)}$-estrene-17α-ol which was used as is for the next step. The product contained a small amount of the 5β,10β-epoxy compound.

STEP C: 3,3-dimethoxy-11β-[4-(N,N-dimethylamino)-phenyl]-17β-ethynyl-Δ^{9}-estrene-5α,17α-diol

A mixture of 2.8 g of the product of Step B, 56 ml of anhydrous tetrahydrofuran and 80 mg of anhydrous copper chloride was stirred under an inert atmosphere at room temperature for 5 minutes and was then placed in an ice bath. 33 ml of 0.95 M 4-dimethylaminophenyl magnesium bromide in tetrahydrofuran were added dropwise to the mixture which was then allowed to return to room temperature.

63 ml of 4-dimethylaminophenyl magnesium bromide were added to a suspension of 6.15 g of dimethylsulfide-copper bromide complex in 30 ml of anhydrous tetrahydrofuran while keeping the temperature below 28.5° C. and the mixture was stirred for 30 minutes. Then, the above solution was added dropwise thereto and the mixture was stirred at room temperature for 18 hours and was then poured into aqueous saturated ammonium chloride solution. The mixture was stirred for 10 minutes and was extracted with chloroform. The organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel and was eluted with a 1-1 petroleum ether-ethyl acetate mixture containing 0.5 ppm of triethylamine. The 1.28 g of product was chromatographed over silica gel and was eluted with the same mixture to obtain 0.84 g of 3,3-dimethoxy-11β-[4-(N,N-dimethylamino)-phenyl]-17β-ethynyl-Δ^{9}-estrene-5α,17α-diol.

STEP D: 11β-[4-(N,N-dimethylamino)-phenyl]-17β-ethynyl-$\Delta^{4,9}$-estradiene-17α-ol-3-one

A mixture of 0.76 g of the product of Step C, 15 ml of methanol and 1.6 ml of 2 N hydrochloric acid was stirred for 90 minutes and was then poured into an aqueous saturated sodium bicarbonate solution. The mixture was extracted with chloroform and the organic phase was dried and evaporated to dryness under reduced pressure. The 0.76 g of residue was chromatographed over silica gel and was eluted with a 1-1 petroleum ether-ethyl acetate mixture and then with a 3-1 ether-petroleum ether mixture to obtain 0.435 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17β-ethynyl-$\Delta^{4,9}$-estradiene-17α-ol-3-one which after crystallization from isopropyl ether melted at 142° C. and had a specific rotation of $[\alpha]_D^{20} = +235.5° \pm 4.5°$ (c=0.45% in chloroform).

EXAMPLE 7

11β-[4-(N,N-dimethylamino)-phenyl]-17α-phenyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-$\Delta^{9(11)}$-estrene-17-one

2 drops of pyridine were added to a mixture of 11.18 g of 3,3-[1,2-ethanediyl-bisoxy]-$\Delta^{9(10),9(11)}$-estradiene-17-one and 56 ml of methylene chloride and 4.3 ml of hexafluoroacetone sesquihydrate were added to the mixture at 0° C. 1.6 ml of 85% oxygenated water were added to the mixture and the mixture was stirred under an inert atmosphere at 0° C. for 23 hours and was poured into a mixture of 200 g of ice and 200 ml of 0.5 M sodium thiosulfate solution. The mixture was stirred for 30 minutes and was extracted with methylene chloride containing a trace of pyridine. The organic phase was washed with water, dried and evaporated to dryness to obtain 11.4 g of 3,3-[1,2-ethanediyl-bisoxy]5α,10α-epoxy-$\Delta^{9(11)}$-estrene-17-one which was used as is for the next step.

STEP B: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-Δ^{9}-estrene-5α-ol-17-one

A mixture of 200 g of 4-dimethylamino benzene bromide in 950 ml of anhydrous tetrahydrofuran was added over 2½ hours at 35° C.±5° C. to a mixture of 29 g of magnesium turnings and 50 ml of anhydrous tetrahydrofuran under an inert atmosphere to obtain a solution of 0.8 M of magnesium.

284 ml of the said magnesium solution were added dropwise over 75 minutes at 0° to 5° C. under an inert atmosphere to a mixture of 25 g of the product of Step A, 500 ml of anhydrous tetrahydrofuran and 0.757 g of copper chloride and the mixture was stirred for 15 minutes and poured into aqueous saturated ammonium chloride solution. The mixture was extracted with ethyl acetate and the organic phase was washed with aqueous saturated ammonium chloride solution and with aqueous saturated sodium chloride solution, dried and evaporated to dryness under reduced pressure. The 46 g of residue were chromatographed over silica gel and were eluted with a 1-1 petroleum ether-ethyl acetate mixture containing 1 ppm of triethylamine to obtain 17.76 g of product melting at 178° C. The impure fractions were subjected again to chromatography over silica gel and were eluted with an 8-2 petroleum ether-acetone mixture containing 1 ppm of triethylamine to obtain another 6.35 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl[-Δ^{9}-estrene-5α-ol-17-one melting at 176° C. which was used as is for the next step.

STEP C: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl[-17α-phenyl-Δ^{9}-estrene-5α,17β-diol

A solution of 4.51 g of the product of Step B in 45.1 ml of anhydrous tetrahydrofuran was added over 30 minutes at 25° C. to a solution of 33.3 ml of phenyllithium (1.5 moles) and the mixture was stirred for 4 hours at room temperature and was then poured into aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The 5.6 g of residue were chromatographed over silica gel and were eluted with a 9-1 methylene chloride-acetone mixture containing 1 ppm of triethylamine to obtain 1.16 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-phenyl-Δ^{9}-estrene-5α,17β-diol which after crystallization from an isopropyl ether-methylene chloride mixture melted at 240° C. and had a specific rotation of $[\alpha]_D^{20} = +53° \pm 2.5°$ (c=0.5 in $CHCl_3$).

STEP D: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-phenyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

3 ml of 2 N hydrochloric acid were added under an inert atmosphere at 0° to 5° C. to a mixture of 1.5 g of the product of Step C in 45 ml of methanol and the mixture was stirred at 0° to 5° C. for one hour. Then, 90 ml of ether and 90 ml of an aqueous 0.25 M of sodium bicarbonate solution were added to the mixture and the mixture was stirred for 5 minutes. The decanted aque-

ous phase was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The 1.3 g of residue were chromatograhed over silica gel and were eluted with a 1-1 petroleum ether ether mixture to obtain 0.93 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-phenyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one which after crystallization from methylene chloride-isopropyl ether melted at 226° C. and had a specific rotation of $[\alpha]_D^{20} = +151.5°$ (c=0.4% in chloroform).

EXAMPLE 8

11β-[4-(N,N-dimethylamino)-phenyl]-23-methyl-19,21-dinor-17α-$\Delta^{4,9,23}$ cholatriene-20-yn-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-23-methyl-19,21-dinor-17α-$\Delta^{9,23}$-choladiene-20-yn-5α,17β-diol

10.61 ml of 2-methyl-1-buten-3-yne were added under an inert atmosphere to a mixture of 4.5 g of potassium tert.-butylate in 90 ml of anhydrous tetrahydrofuran and the mixture was stirred for 15 minutes at −10° C. A solution of 4.5 g of the product of Step B of Example 7 in 45 ml of anhydrous tetrahydrofuran was added over 15 minutes to the reaction mixture and the mixture was stirred at −10° C. for 30 minutes and then for 4 hours at 0° to 5° C. The mixture was poured into 500 ml of aqueous saturated solution of ammonium chloride and the mixture was extracted with ethyl acetate. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness to obtain 5.56 g of raw 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-23-methyl-19,21-dinor-17α-$\Delta^{9,23}$-choladiene-20-yn-5α,17β-diol melting at 205° C. which was used as is for the next step. The raw product was chromatographed over silica gel and was eluted with a 9-1 methylene chloride-ethyl acetate containing 1 ppm of triethylamine and crystallized from ethyl acetate to obtain the product melting at 215° C.

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-23-methyl-19,21-dinor-17α-$\Delta^{4,9,23}$-cholatriene-20-yne-17β-ol-3-one

A mixture of 5 g of the product of Step A, 300 ml of methanol and 10 ml of 2 N hydrochloric acid was stirred under an inert atmosphere for 15 minutes at 20° C. and then 300 ml of methylene chloride and then 300 ml of aqueous 0.25 M sodium bicarbonate solution were added thereto. The mixture was stirred for 10 minutes and the decanted aqueous phase was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness. The 4.5 g of residue were chromatographed over silica gel and were eluted with a 1-1 petroleum ether-ethyl acetate mixture to obtain after crystallization from diisopropyl oxide 2.01 g of 11β-[4-(N,N-dimethylamino)-phenyl]-23-methyl-19,21-dinor-17α-$\Delta^{4,9,23}$-cholatriene-20-yne-17β-ol-3-one melting at 185° C. and having a specific rotation of $[\alpha]_D^{20} = +88.5° \pm 1.5°$ (c=1% in $CHCl_3$).

EXAMPLE 9

11β-[4-(N,N-dimethylamino)-phenyl]-17β-methoxy-23-methyl-19,21-dinor-17α-$\Delta^{4,9,23}$-cholatriene-20-yne-3-one

10.61 ml of 2-methyl-1-buten-3-yne were added dropwise at −10° C. to a suspension of 4.5 g of potassium tert.-butylate in 90 ml of anhydrous tetrahydrofuran under an inert atmosphere and the mixture was stirred at −10° C. for 15 minutes. Then, a mixture of 4.5 g of the product of Step B of Example 7 in 45 ml of anhydrous tetrahydrofuran was added over 15 minutes to the mixture which was then stirred at −10° C. for 30 minutes and at 0° to 5° C. for 4 hours. 7.5 ml of methyl iodide were added to the mixture which was then stirred in an ice bath for 30 minutes and then poured into 500 ml of 0.1 N hydrochloric acid. The mixture was stirred for 30 minutes at room temperature and was then extracted with ethyl acetate. The organic phase was washed with aqueous saturated sodium bicarbonate solution, then with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 95-5 methylene chloride-ethyl acetate mixture to obtain 2.7 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17β-methoxy-23-methyl-19,21-dinor-17α-$\Delta^{4,9,23}$-cholatriene-20-yne-3-one which after crystallization from methanol melted at 105° C.

EXAMPLE 10

11β-[4-(N,N-dimethylamino)-phenyl]21-chloro-19-nor-17α-$\Delta^{4,9}$-pregnadiene-20-yne-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^{9}-pregnene-20-yne-5α,17β-diol

A solution of 7 ml of trichloroethylene in 28 ml of anhydrous ether was added with stirring under an inert atmosphere at 0° to 5° C. to a mixture of 77.5 ml of 1 M butyllithium in hexane and 310 ml of anhydrous ether and the mixture was stirred for one hour while the temperature rose to 20° C. A solution of 7 g of Step B of Example 7 in 70 ml of tetrahydrofuran was added to the resulting mixture dropwise over 30 minutes at 0° to 5° C. and the mixture was stirred at 0° to 5° C. for 30 minutes after which the temperature was allowed to rise to 20° C. and was slowly poured into an aqueous saturated ammonium chloride solution and the decanted aqueous phase was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness to obtain 8.5 g of raw product melting at 220° C. The latter was added to 42.5 ml of diisopropyl oxide and the mixture was stirred for 30 minutes and vacuum filtered to obtain 6.38 g of product melting at 230° C. The latter was chromatograhed over silica gel and was eluted with a 7-3 benzene-ethyl acetate mixture containing 1 ppm of triethylamine. The product was dissolved in methylene chloride and was precipitated by addition of diisopropyl oxide to obtain 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^{9}-pregnene-20-yne-5α,17β-diol melting at 240° C. and having a specific rotation of $[\alpha]_D^{20} = -83.5° \pm 1.5°$ (c=1% in $CHCl_3$).

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-$\Delta^{4,9}$-pregnadiene-20-yne-17β-ol-3-one

15 ml of 2 N hydrochloric acid were added under an inert atmosphere to a mixture of 6.38 g of the product of Step A in 191.4 ml of 95% ethanol and after stirring the mixture for one hour, 300 ml of methylene chloride and then 200 ml of aqueous 0.25 mm sodium bicarbonate solution were added thereto. The decanted aqueous phase was extracted with methylene chloride and the organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The 6 g of residue were chromatographed over silica gel and were eluted with a 7-3 benzene-ethyl acetate mixture to ob-

tain 3.95 g of 11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ4,9-pregnadiene-20-yne-17β-ol-3-one which after crystallization from ethyl acetate melted at 240° C. and had a specific rotation of $[\alpha]_D^{20} = +111° \pm 2°$ (c = 1% in chloroform).

EXAMPLE 11

N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ4,9-pregnadiene-20-yne-17β-ol-3-one

A mixture of 0.54 g of 85% M-chloroperbenzoic acid in 10.8 ml of methylene chloride was added under an inert atmosphere at 0° to 5° C. to a mixture of 1.2 g of the product of Example 10 in 24 ml of methylene chloride and the mixture was stirred for one hour at 0° to 5° C. and was then poured into aqueous 0.2 N sodium thiosulfate solution. The mixture was extracted with methylene chloride and the organic phase was washed with aqueous saturated sodium bicarbonate solution, with water, dried and evaporated to dryness. The 1.3 g of residue was chromatographed over silica gel and was eluted with a 7-3 methylene chloride-methanol mixture to obtain 1.15 g of N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ4,9-pregnadiene-20-yne-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +47.5° \pm 1.5°$ (c = 0.7% in chloroform).

EXAMPLE 12

N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-9α,10α-epoxy-21-chloro-19-nor-17α-Δ4-pregnene-20-yne-17β-ol-3-one

A mixture of 1.17 g of 85% m-chloroperbenzoic acid in 23.4 ml of methylene chloride was added over 15 minutes at 0° to 5° C. to a solution of 1.18 g of the product of Example 10 in 23.6 ml of methylene chloride and the mixture was stirred for 2 hours at 20° C. after which another 1.17 g of 85% M-chloroperbenzoic acid were added. The mixture was stirred for one hour and was poured into a solution of aqueous 0.2 N sodium thiosulfate. The mixture was extracted with methylene chloride and the organic phase was washed with aqueous saturated sodium bicarbonate solution and then with water, dried and evaporated to dryness to obtain 1.14 g of residue melting at 220° C. The residue was chromatographed over silica gel and was eluted with an 8-2 methylene chloride-methanol mixture to obtain 1 g of N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-9α,10α-epoxy-21-chloro-19-nor-17α-Δ4-pregnene-20-yne-17β-ol-3-one melting at 270° C. and having a specific rotation of $[\alpha]_D^{20} = +39.5° \pm 2.5°$ (c = 0.5% in chloroform).

EXAMPLE 13

9α,10α-epoxy-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ4-pregnene-20-yne-17β-ol-3-one

0.34 g of triphenylphosphine were added under an inert atmosphere to a mixture of 0.63 g of the product of Example 12 in 6.3 ml of acetic acid and the mixture was stirred at room temperature for 45 minutes and was then poured into water. The mixture was extracted with methylene chloride and the organic phase was washed with water, dried and evaporated to dryness. The 0.9 g of residue was chromatographed over silica gel and was eluted with a 1-1 petroleum ether-ethyl acetate mixture. The product was crystallized from a methylene chloride-isopropyl ether mixture to obtain 0.346 g of 9α,10α-epoxy-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ4-pregnene-20-yne-17β-ol-3-one melting at 265° C. and having a specific rotation of $[\alpha]_D^{20} = +45° \pm 2°$ (c = 0.8% in chloroform).

EXAMPLE 14

11β-[4-(N,N-dimethylamino)-phenyl]-21-phenyl-19-nor-17α-Δ4,9-pregnadiene-20-yne-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-phenyl-19-nor-17α-Δ9-pregnene-20-yne-5α,17β-diol

A mixture of 4.17 g of potassium tert.-butylate in 83 ml of anhydrous tetrahydrofuran was stirred under an inert atmosphere for 10 minutes and then 4.5 ml of phenyl acetylene were added dropwise at −10° C. The suspension was stirred for 5 minutes and then a solution of 4.17 g of the product of Step B of Example 7 in 41 ml of anhydrous tetrahydrofuran was added thereto dropwise at −10° C. Then, the temperature rose to 0° C. and held there for one hour and was then poured into an aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The 4.7 g of residue were chromatographed over silica gel and eluted with a 95-5 methylene chloride-acetone mixture to obtain 3.71 of of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4,(N,N-dimethylamino-phenyl]-21-phenyl-19-nor-17α-Δ9-pregnene-20-yne-5α,17β-diol melting at 168° C. and having a specific rotation of $[\alpha]_D^{20} = -119.5° \pm 2°$ (c = 1% in chloroform).

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-21-phenyl-19-nor-17α-Δ4,9-pregnadiene-20-yne-17β-ol-3-one

6.3 ml of 2 N hydrochloric acid were added to a solution of 3.49 g of the product of Step A in 68 ml of methanol and the mixture was stirred for 30 minutes and was poured into a mixture of 180 ml of ether and 90 ml of aqueous 0.25 M sodium bicarbonate solution. The mixture was stirred for 5 minutes and the decanted aqueous phase was extracted with ether. The organic phase was washed with aqueous 0.25 M sodium bicarbonate solution, then with aqueous sodium chloride, dried and evaporated to dryness. The 4.35 g of residue were chromatographed over silica gel and eluted with with a 95-5 methylene chloride-acetone mixture to obtain 2.13 g of 11β-[4-(N,N-dimethylamino)-phenyl]-21-phenyl-19-nor-17α-Δ4,9-pregnadiene-20-yne-17β-ol-3-one which after crystallization from isopropyl ether had a specific rotation of $[\alpha]_D^{20} = +22.5° \pm 1°$ (c = 1% in chloroform).

EXAMPLE 15

11β-[4-(N,N-dimethylamino)-phenyl]-17α-(propa-1,2-dienyl)-Δ4,9-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)phenyl]-17α-(propa-1,2-dienyl)-Δ9-estrene-5α,17β-diol and 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-Δ9-estrene-5α,17β-diol

Allene was bubbled into 50 ml of anhydrous tetrahydrofuran at 0° to 5° C. until 2.1 g were absorbed and 23.9 ml of a solution of a 1.3 M of butyllithium in hexane were added thereto over 15 minutes at −70° C. The mixture was stirred at −70° C. for 15 minutes and then a solution of 3.5 g of the product of Step B of Example 7 in 35 ml of anhydrous tetrahydrofuran were added

thereto at −70° C. over 25 minutes. The mixture was stirred at −70° C. for one hour and was poured slowly into an iced aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The 3.4 g of residue were chromatographed over silica gel and eluted with a 1-1 petroleum ether-ethyl acetate mixture containing 1 ppm of triethylamine to obtain 1.73 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(propa-1,2-dienyl)-Δ^9-estrene-5α,17β-diol melting at 178° C. and having a specific rotation of $[\alpha]_D^{20} = -32° \pm 2°$ (c=0.7% in chloroform) and 1.5 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-Δ^9-estrene-5α,17β-diol melting at 150° C. and having a specific rotation of $[\alpha]_D^{20} = -15° + 2°$ (c=0.9% in chloroform).

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(propa-1,2-dienyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A mixture of 1.73 g of the 17α-(propa-1,2-dienyl)-isomer of Step A, 51.8 ml of 95% ethanol and 3.5 ml of 2 N hydrochloric acid was stirred under an inert atmosphere at 20° C. for one hour and then 50 ml of methylene chloride and 50 ml of aqueous 0.25 M sodium bicarbonate solution were added thereto. The decanted aqueous phase was extracted with methylene chloride and the organic phase was washed with water, dried and evaporated to dryness. The 1.51 g of residue were dissolved in 10 ml of hot methylene chloride and 15 ml of isopropyl ether were added to the solution. The mixture was concentrated and allowed to stand to obtain 1.23 g of product which were crystallized form a methylene chloride-isopropyl ether mixture to obtain 1.11 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(propa-1,2-dienyl)-$\Delta^{4,9}$-estradiene 17β-ol-3-one melting at 228° C. and having a specific rotation of $[\alpha]_D^{20} = +139.5° \pm 3°$ (c=0.8% in chloroform).

EXAMPLE 16

11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A mixture of 0.94 g of the 17α-(prop-2-ynyl)-isomer of Step A of Example 15, 28.2 ml of 95% ethanol and 2 ml of 2 N hydrochloric acid was stirred at 20° C. for one hour and then 50 ml of methylene chloride and 50 ml of an aqueous 0.25 M sodium bicarbonate solution were added thereto. The mixture was stirred for 5 minutes and the decanted aqueous phase was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness and the residue was chromatographed over silica gel. Elution with a 1-1 petroleum ether-ethyl acetate mixture yielded 0.42 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +143° \pm 3°$ (c=0.8% in chloroform).

EXAMPLE 17

11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-$\Delta^{4,9}$-estradiene 17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17β-cyano-17α-trimethylsilyloxy-Δ^9-estrene-5α-ol

A solution of 18 mmoles of [4-(N,N-dimethylamino)-phenyl]-magnesium bromide in anhydrous tetrahydrofuran was added under an inert atmosphere to a suspension of 2.05 g of dimethylsulfide-copper bromide complex in 10 ml of anhydrous tetrahydrofuran and the mixture was stirred for 30 minutes after which 20 ml of anhydrous triethylamine were added thereto. A solution of 0.95 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17β-cyano-17α-trimethylsilyloxy-$\Delta^{9(11)}$-estrene in anhydrous tetrahydrofuran were added to the mixture which was then stirred for 15 hours at room temperature and poured into 50 ml of aqueous saturated ammonium chloride solution. The decanted aqueous phase was extracted with ether and the organic phase was washed with water, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with an 8-2 benzene-ethyl acetate mixture to obtain 1.1 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17β-cyano-17α-trimethylsilyloxy-Δ^9-estrene-5α-ol which after crystallization from isopropyl ether melted at 247° C. and had a specific rotation of $[\alpha]_D^{20} = -12.5°$ (c=1% in chloroform).

STEP B: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-Δ^9-estrene-5α,17β-diol

1 g of the acetylide complex of lithium ethylenediamine was added to a mixture of 0.8 g of the product of Step A in 8 ml of ethylenediamine and the mixture was stirred under an inert atmosphere at −50° C. for 90 minutes. The mixture was cooled to 20° C. and was poured into aqueous ammonium chloride solution. The mixture was extracted with ether and methylene chloride and the organic phase was dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 7-3 benzene-ethyl acetate mixture. The product was crystallized from isopropyl ether to obtain 0.43 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-Δ^9-estrene-5α,17β-diol melting at 199° C. and having a specific rotation of $[\alpha]_D^{20} = -43° \pm 1.5°$ (c=1% in chloroform).

STEP C: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

1 ml of 2 N hydrochloric acid was added to a solution of 0.25 g of the product of Step B in 6 ml of methanol and the mixture was stirred at 20° C. for 40 minutes and then was poured into water containing 2.5 ml of N sodium hydroxide. The mixture was extracted with ether and the organic phase was dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 7-3 benzene-ethyl acetate mixture to obtain 0.25 of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one.

Analysis: $C_{32}H_{33}NO_2$; molecular weight=415.54 Calculated: %C, 80.92; %H, 8.00; %N, 3.37. Found: %C, 80.7; %H, 8.1; %N, 3.1.

EXAMPLE 18

11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-Δ^9-estrene-5α,17β-diol

12.25 g of the acetylide complex of lithium ethylenediamine were added under an inert atmosphere to a solution of 6 g of the product of Step B of Example 7 in 180 ml of tetrahydrofuran and the mixture was stirred at 55° C. for 4 hours and was then cooled and poured into

600 ml of an iced aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and eluted with a 7-3 benzene-ethyl acetate mixture containing 1 ppm of triethylamine. The 4.5 g of product was crystallized from a methylene chloride-diisopropyl oxide mixture to obtain 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-Δ^{9} -estrene-5α,17β-diol melting at 202° C. and having a specific rotation of $[\alpha]_D^{20} = -47.5° \pm 1.5°$ (c = 1% in chloroform).

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-Δ^{4,9}-estradiene-17β-ol-3-one

5 ml of 2 N hydrochloric acid were added to a suspension of 2 g of the product of Step A in 50 ml of 95% ethanol and the mixture was stirred at 20° C. for one hour. 100 ml of ether and then 100 ml of aqueous 0.25 M sodium bicarbonate solution were added to the mixture and the decanted aqueous phase was extracted with ether. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness and the residue was chromatographed over silica gel. Elution with a 6-4 petroleum ether-ethyl acetate mixture yielded 1.52 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-Δ^{4,9}-estradiene-17β-ol-3-one which after crystallization from diisopropyl oxide melted at 172° C. and had a specific rotation of $[\alpha]_D^{20} = +182° \pm 2.5°$ (c = 1% in chloroform).

EXAMPLE 19

11β-[3-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[3-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

A mixture of 10 g of m-bromo-dimethylaniline in 45 ml of anhydrous tetrahydrofuran was added under an inert atmosphere over 45 minutes to a mixture of 1.46 g of magnesium and 5 ml of anhydrous tetrahydrofuran and the reaction was started by addition of dibromomethane. The mixture was stirred for one hour to obtain a solution of 0.95 M of magnesium and 42.2 ml of the solution were added at 0° to 5° C. over 30 minutes under an inert atmosphere to a mixture of 3.7 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-Δ$^{9(11)}$-estrene-17β-ol, 74 ml of anhydrous tetrahydrofuran and 99 mg of copper chloride and the mixture was stirred for 30 minutes at 0° to 5° C. and was poured into an aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and eluted with a 9-1 methylene chloride-acetone mixture containing 1 ppm of triethylamine to obtain 3.5 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[3-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol melting at 262° C. and having a specific rotation of $[\alpha]_D^{20} = -64° \pm 1.5°$ (c = 1% in chloroform) and 0.66 g of the corresponding 5β-ol isomer melting at 210° C. and having a specific rotation of $[\alpha]_D^{20} = +32.5° \pm 1°$ (c = 0.8% in chloroform).

STEP B: 11β-[3-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one

10 ml of 2 N hydrochloric acid were added at 0° to 5° C. under an inert gas to a mixture of 3.1 g of the product

of step A in 100 ml of methanol and the mixture was stirred at 0° to 5° C. for one hour. 200 ml of diethyl oxide and then 200 ml of aqueous 0.25 M sodium bicarbonate solution were added to the mixture which was then stirred for 5 minutes. The decanted aqueous phase was extracted with diethyloxide and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The 3 g of residue were chromatographed over silica gel and eluted with a 7-3 benzene-ethyl acetate mixture to obtain 1.43 g of amphorous 11β-[3-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +43° \pm 2.5°$ (c = 1% in $CHCl_3$).

EXAMPLE 20

N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one

A solution of 0.71 g of 85% m-chloroperbenzoic acid in 14.2 ml of methylene chloride was added over 10 minutes at 0° to 5° C. to a mixture of 1.5 g of the product of Example 4 in 30 ml of methylene chloride and the mixture was stirred for one hour at 0° to 5° C. and was poured into 100 ml of an aqueous 0.2 N sodium thiosulfate solution. The decanted aqueous phase was extracted with methylene chloride and the organic phase was washed with aqueous 0.5 M sodium bicarbonate solution, dried and evaporated to dryness. The residue was dissolved in 20 ml of methylene chloride and 20 ml of diisopropyl oxide were added thereto. Crystallization was induced and the mixture stood for a while and was vacuum filtered. The crystals were dried to obtain 1.4 g of N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one melting at 210° C. and having a specific rotation of $[\alpha]_D^{20} = +73.5° \pm 2°$ (c = 1% in chloroform).

EXAMPLE 21

11β-[4-(N,N-dimethylamino)-phenyl]-Δ^{4,9}-estradiene-17β-ol-3-one

106 mg of sodium borohydride were added to a solution of 1 g of the product of Step B of Example 7 in 20 ml of tetrahydrofuran containing 10% water and the mixture was stirred for one hour and poured into 200 ml of water. The mixture was extracted with methylene chloride and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness to obtain 1.3 g of 11β-[4-(N,N-dimethylamino)-phenyl]-Δ^{4,9}-estradiene-5α,17β-diol-3-one. 0.63 g of the latter were added to a mixture of 12 ml of methanol and 2.4 ml of 2 N hydrochloric acid and the mixture was stirred at room temperature for 90 minutes and was poured into aqueous sodium bicarbonate. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 6-4 petroleum ether-ethyl acetate mixture. The residue was triturated with petroleum ether and vacuum filtered to obtain 0.38 g of 11β-[4-(N,N-dimethylamino)-phenyl]-Δ^{4,9}-estradiene-17β-ol-3-one melting at 130° C. and having a specific rotation of $[\alpha]_D^{20} = +277° \pm 5°$ (c = 0.5% in chloroform).

EXAMPLE 22

11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-enyl)-Δ^{4,9}-estradien-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-enyl)-Δ^{9}-estrene-5α,17β-diol

A solution of 3.5 g of the product of Step B of Example 7 in 35 ml of tetrahydrofuran was added under an inert atmosphere at 20° C. over 15 minutes to 55.5 ml of 0.7 M allyl magnesium bromide in ether and the mixture was stirred at 20° C. for one hour and was then poured into an aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was dissolved in 10 ml of methylene chloride and 15 ml of diisopropyl oxide were added to the solution which was then concentrated and allowed to stand. The mixture was vacuum filtered and the crystals were rinsed with diisopropyl oxide and dried to obtain 2.76 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-enyl)-Δ^{9}-estrene-5α,17β-diol melting at 198° C.

Analysis: $C_{31}H_{43}NO_4$; molecular weight = 493.69 Calculated: %C, 74.42; %H, 8.78; %N, 2.83. Found: %C, 74.0; %H, 8.7; %N, 2.9.

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-enyl)-Δ^{4,9}-estradiene-17β-ol-3-one

4.5 ml of 2 N hydrochloric acid were added to a suspension of 2.2 g of the product of Step A in 66 ml of methanol and the mixture was stirred at 20° C. for 30 minutes after which 132 ml of diethyl oxide and then 132 ml of aqueous 0.25 M sodium bicarbonate solution were added thereto. The decanted aqueous phase was extracted with diethyl oxide and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 7-3 benzene-ethyl acetate mixture. The product was taken up in a mixture of 15 ml of diisopropyl oxide and 7.5 ml of methylene chloride and the solution was concentrated and allowed to stand. The mixture was vacuum filtered and the crystals were rinsed with diisopropyl oxide and dried to obtain 1.365 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-enyl)-Δ^{4,9}-estradiene-17β-ol-3-one melting at 182° C. and having a specific rotation of $[\alpha]_D^{20} = +206.5° \pm 3°$ (c = 1% in chloroform).

EXAMPLE 23

11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

A solution of 42.8 g of 4-(N,N-dimethylaminomethyl)bromobenzene in 190 ml of anhydrous tetrahydrofuran was added over 90 minutes under an inert atmosphere at 45° to 50° C. to a mixture of 5.5 g of magnesium in 10 ml of anhydrous tetrahydrofuran and the reaction was induced with dibromoethane addition. The mixture was stirred for one hour to obtain an 0.85 M magnesium solution and 127 ml of the said solution were added under an inert atmosphere at 0° to 5° C. over one hour to a mixture of 10 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-Δ$^{9(11)}$-estrene-17β-ol, 200 ml of anhydrous tetrahydrofuran and 0.27 g of copper chloride. The mixture was stirred for 15 minutes and was poured into an aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 9-1 methylene chloride-methanol mixture containing 1 ppm of triethylamine to obtain 10.1 g of product. The latter was dissolved in methylene chloride and a few drops of methanol and then diisopropyl oxide were added thereto. The mixture was concentrated, allowed to stand for 6 hours and was vacuum filtered to obtain 7.37 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol melting at 186° C. and having a specific rotation of $[\alpha]_D^{20} = -63° \pm 2.5°$ (c = 0.5% in chloroform).

STEP B: 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one

A mixture of 15 ml of 2 N hydrochloric acid, 7.37 g of the product of Step A and 147.4 ml of methanol was stirred at 20° C. for one hour and then 300 ml of diethyl oxide and 300 ml of aqueous 0.25 M sodium bicarbonate solution were added thereto. The decanted aqueous phase was extracted with diethyl oxide and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The product was dissolved in a mixture of diisopropyl oxide and methylene chloride and the solution was concentrated and allowed to stand. The mixture was vacuum filtered and the crystals were dried to obtain 3.74 g of 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one melting at 190° C. and having a specific rotation of $[\alpha]_D^{20} = +84.5° \pm 2°$ (c = 0.8% in chloroform).

EXAMPLE 24

11β-(4-pyrrolidinyl-phenyl)-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxyl]-11β-(4-pyrrolidinylphenyl)-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

A solution of 34 g of 4-pyrrolidinyl-bromobenzene in 140 ml of anhydrous tetrahydrofuran was added over one hour under an inert atmosphere at 45°-50° C. to a mixture of 4 g of magnesium and 10 ml of anhydrous tetrahydrofuran and the reaction was started by addition of dibromoethane to obtain a 1 M magnesium solution. 86.4 ml of the said solution were added over 90 minutes at 0° to 5° C. under an inert atmosphere to a mixture of 8 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-Δ$^{9(11)}$-estrene-17β-ol in 160 ml of anhydrous tetrahydrofuran and 216 mg of copper chloride and the mixture was stirred for one hour and was poured into an aqueous saturated ammonium chloride solution. The mixture was extracted with diethyl oxide and the organic phase was washed with aqueous saturated ammonium chloride solution, aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 95-5 methylene chloride-acetone mixture containing 1 ppm of triethylamine to obtain 8.3 g of 3,3-[1,2-ethanediylbisoxyl]-11β-(4-pyrrolidinyl-phenyl)-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol which after crystallization from a methylene chlo-

EXAMPLE 29

11β-[4-(N,N-dimethylamino)-phenyl]-21-trimethylsilyl-19-nor-17β-Δ^{4,9}-pregnadiene-20-yne-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-trimethylsilyl-19-nor-17α-Δ^{9}-pregnene-20-yne-5α,17β-diol

A mixture of 13 ml of a 1.6 M ethyl magnesium bromide in tetrahydrofuran and 13 ml of anhydrous tetrahydrofuran was stirred for 5 minutes at 0° to 5° C. and 3.4 ml of trimethylsilyl acetylene were added thereto dropwise. The temperature was allowed to rise to 20° C. and the mixture was then stirred for 20 minutes. Then, a solution of 1.12 g of the product of Step B of Example 7 in 10 ml of anhydrous tetrahydrofuran was added dropwise to the mixture and the mixture was stirred at room temperature for 16 hours and was poured into aqueous ammonium chloride solution. The mixture was stirred at room temperature for 10 minutes and was extracted with methylene chloride. The organic phase was washed with aqueous saturated sodium chloride solution, was dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 6-4 petroleum ether-ethyl acetate mixture to obtain 680 mg of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-trimethylsilyl-19-nor-17α-Δ^{9}-pregnene-20-yne-5α,17β-diol with a specific rotation of $[\alpha]_D^{20} = -76.5° \pm 3°$ (c=0.5% in chloroform).

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-21-trimethylsilyl-19-nor-17α-Δ^{4,9}-pregnadiene-20-yne-17β-ol-3-one

A mixture of 1 ml of 2 N hydrochloric acid, 562 mg of the product of Step A and 15 ml of methanol was stirred at room temperature for 40 minutes and was poured into aqueous sodium bicarbonate solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, was dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 6-4 petroleum ether-ethyl acetate mixture to obtain 364 mg of 11β-[4-(N,N-dimethylamino)-phenyl]-21-trimethylsilyl--19-nor-17α-Δ^{4,9}-pregnadiene--20-yne-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +97.5° \pm 3°$ (c=0.35% in $CHCl_3$).

Analysis: $C_{31}H_{41}NO_2Si$; molecular weight=487.76 Calculated: %C, 76.33; %H, 8.47; %N, 2.87. Found: %C, 76.4; %H, 8.7; %N, 2.8.

EXAMPLE 30

N-oxide of 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)]-Δ^{4,9}-estradiene-17β-ol-3-one

A solution of 0.64 g of m-chloroperbenzoic acid in 12.8 ml of methylene chloride was added over 15 minutes at 0° to 5° C. to a solution of 1.4 g of the product of Example 23 in 28 ml of methylene chloride and the mixture was stirred at 0° to 5° C. for one hour and was then poured into aqueous 0.2 N sodium thiosulfate solution. The decanted aqueous phase was extracted with methylene chloride and the organic phase was washed with aqueous sodium bicarbonate solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with an 8-2 mixture to obtain 1.28 g of N-oxide of 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one. The product was dissolved in a mixture of methylene chloride and diisopropyl oxide and the mixture was vacuum filtered to obtain 1.075 g of the said product melting at 215° C. and having a specific rotation of $[\alpha]_D^{20} = +74.5° \pm 2.5°$ (c=0.7% in $CHCl_3$).

EXAMPLE 31

Hemifumarate of 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one

A mixture of 0.37 g of fumaric acid in 4.54 ml of ethanol was added to a mixture of 1.44 g of the product of Example 23 in 2.88 ml of ethanol and the mixture was stirred at 60° C. for 30 minutes. The mixture returned to 20° C. and was stirred. The mixture was evaporated to dryness and the residue was taken up in ether. The mixture was vacuum filtered and the product was dried to obtain 1.70 g of hemifumarate of 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one melting at 160° C. and having a specific rotation of $[\alpha]_D^{20} = +70.5° \pm 2.5°$ (c=0.8% in $CHCl_3$).

EXAMPLE 32

11β-[4-(N,N-dipropylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-4-(N,N-dipropylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

A solution of 52 g of 4-bromo-N,N-dipropyl-aniline in 110 ml of tetrahydrofuran was added dropwise at 40° C. under an inert atmosphere to a mixture of 5 g of magnesium and 15 ml of anhydrous tetrahydrofuran to obtain a 1.1 M magnesium solution. A solution of 5.55 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-Δ$^{9(11)}$-estrene-17β-ol and 200 mg of cuprous chloride was stirred at 0° to 5° C. and then 50 ml of the magnesium solution were added thereto over 15 minutes. The mixture was stirred at 20° C. for one hour and was then poured into aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 7-3 toluene-ethyl acetate mixture to obtain 6.3 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dipropylamino]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α, 17β-diol with a specific rotation of $[\alpha]_D^{20} = -56° \pm 2°$ (c=0.8% in $CHCl_3$).

Analysis: $C_{35}H_{49}NO_4$; molecular weight =547.75 Calculated: %C, 76.74; %H, 9.02; %N, 2.56. Found: %C, 76.6; %H, 9.2; %N, 2.5.

STEP B: 11β-[4-(N,N-dipropylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one

A mixture of 10 ml of 2 N hydrochloric acid, 5.83 g of the product of Step A and 80 ml of methanol was stirred at 20° C. for 50 minutes and was then neutralized by addition of N sodium hydroxide solution. The mixture was evaporated to dryness under reduced pressure and the residue was taken up in methylene chloride. The organic phase was washed with water, dried and evaporated to dryness and the residue was chromatographed over silica gel. Elution with a 3-1 toluene-ethyl acetate mixture yielded 3.81 g of 11β-[4-(N,N-dipropylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{4,9}-estradiene-17β-ol-3-one.

IR Spectrum: Absorption at 3600 cm^{-1} (OH); at 1654 cm^{-1} (C=O); at 1610-1595-1558 and 1517 cm^{-1} ($\Delta^{4,9}$ and aromatic bands); at 2240 cm^{-1} (C≡C).

The following products were prepared by the process of the invention using the appropriate starting materials:

(A) 11β-[4-(N-ethyl-N-methylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one melting at 174° C. and having a specific rotation of $[\alpha]_D^{20} = +149° \pm 2.5°$ (c=1% in $CHCl_3$).

(B) 11β-[N-methyl-2,3-dihydro-1H-indol-5-yl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one melting at 176° C. and having a specific rotation of $[\alpha]_D^{20} = +133° \pm 3°$ (c=0.8% in $CHCl_3$).

(C) 3-hydroxyimino-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol (Z isomer) melting at 260° and having a specific rotation of $[\alpha]_D^{20} = +141° \pm 3.5°$ (c=0.8% in $CHCl_3$) and the corresponding E isomer melting at 220° C. and having a specific rotation of $[\alpha]_D^{20} = +164° \pm 3.5°$ (c=0.8% in $CHCl_3$).

(D) N-oxide of 11β-[4-pyrrolidyl-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one melting at 220° C. and having a specific rotation of $[\alpha]_D^{20} = +88° \pm 2.5°$ (c=0.75% in $CHCl_3$)

(E) 11β-[4-(N-methyl-N-isopropylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +140° \pm 3.5°$ (c=0.5% in $CHCl_3$).

(F) N-oxide of 11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +60.5°$ (c=1.2% in $CHCl_3$).

(G) N-oxide of 11β-[(N-methyl)-2,3-dihydro-1H-indol-5-yl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +103° \pm 2.5°$ (c=0.8% in $CHCl_3$).

(H) 11β-[4-(N-methyl-N-trimethylsilylmethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one.

(I) 11β-[4-(N-methyl-N-dimethylaminoethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one.

(J) 11β-[4-(N-methyl-piperazin-1-yl)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one.

(K) 11β-[4-(N,N-dimethylamino)-phenyl]-17-hydroxyimino-$\Delta^{4,9}$-estradiene-3-one with a specific rotation of $[\alpha]_D^{20} = +207.5° \pm 3.5°$ (c=1% in $CHCl_3$).

(L) 3(E)-hydroxyimino-11β-[4-(N,N-dimethylamino)-phenyl]-D 17-hydroxyimino-$\Delta^{4,9}$-estradiene-3-one with a specific rotation of $[\alpha]_D^{20} = +195° \pm 3°$ (c=1% in $CHCl_3$) and its corresponding 3(Z) isomer with a specific rotation of $[\alpha]_D^{20} = +163° \pm 2.5°$ (c=0.6% in $CHCl_3$).

EXAMPLE 33

Tablets were prepared containing 50 mg of the product of Example 4 and sufficient excipient of talc, starch and magnesium stearate for a final tablet weight of 120 mg.

PHARMACOLOGICAL STUDY

I. Activity of products on hormonal receptors

A. Mineralcorticoidal receptor of kidneys of the rat

Male Sprague-Dawley EOPS rats weighing 140 to 160 g were surrenalectomized 4 to 8 days previously were killed and their kidneys were perfused in situ with 50 ml of a buffer (10 mM of Tris 0.25 M of Saccharose and sufficient hydrochloric acid for a pH of 7.4). The kidneys were then removed, decapsulated and homogenized at 0° C. with of a polytetrafluoroethylene-glass Potter (1 g of tissue per 3ml of buffer). The homogenate was centrifuged for 10 minutes at 800 g at 0° C.

After elimination of the fixation of tritied aldosterone with glucocorticoid receptor, 21-methyl-$\Delta^{1,4,6}$-pregnatriene -20-yne-11β,17β-diol-3-one fixed only with the glucocorticoid receptor was added to the surnageant at a final concentration of 10^{-6}M. The surnageant was ultracentrifuged at 105,000 g for 60 minutes at 0° C. and aliquoits of the resulting surnageant were incubated at 0° C. with a constant concentration (T) of tritied aldosterone in the presence of increasing concentrations (0-2500× 10^{-9} M) of cold aldosterone or the cold test product. After a time (t) of incubation, the concentration of tied tritied aldosterone (B) was measured by the technique of adsorption on carbon-dextran.

B. Androgen receptor of prostate of rats

Male Sprague-Dawley EOPS rats weighing 160 to 200 g were castrated and 24 hours later, the animals were killed. The prostates were removed, weighed and homogenized at 0° C. with a polytetrafluoroethylene-glass Potter with a buffered TS solution (Tris, 10 mM, 0.25 M Saccharose, HCl-pH of 7.4) using 1 g of tissue per 5 ml of TS. The homogenate was then ultracentrifuged at 105,000 g after 60 minutes at 0° C. and aliquoits of the resulting surnageant were incubated at 0° C. for 2 hours with a constant concentration (T) of product P or 17α-methyl-$\Delta^{4,9,11}$-estratriene-17β-ol-3-one in the presence of increasing concentrations (0-1,000× 10^{-9} M) of either cold P, cold testosterone or the test compound. The concentration of tied tritied P (B) was measured for each incubate by the technique of adsorption on carbon-dextran.

C. Progestogen receptor of the uterus of rabbits

Immature rabbits weighing about 1 kg received a cutaneous application of 25 µg of estradiol and the animals were killed 5 days later. The uterus were removed, weighed and homogenized at 0° C. with a polytetrafluoroethylene-glass Potter in a buffered TS solution [Tris 10 mM, 0.25 M of Saccharose, HCl-pH of 7.4] with 1 g of tissue per 50 ml of TS. The homogenate was ultracentrifuged at 105,000 g for 90 minutes at 0° C. and aliquoits of the resulting surnageant were incubated at 0° C. for a time (t) with a constant concentration (T) of tritied product R or 17,21-dimethyl-19-nor-$\Delta^{4,9}$-pregnadiene-3,20-dione in the presence of increasing concentrations (0 to 2500× 10^{-9} M) of either cold R, cold progesterone or cold test compound. The concentration of tied tritied R (B) was then measured for each incubate by the technique of adsorption on carbon-dextran.

D. Gluocorticoid receptor of thymus of rats

Male Sprague-Dawley EOPS rats weighing 160 to 200 g were surrenalectomized and the animals were killed 4 to 8 days later. The thymus were removed and homogenized at 0° C. in a buffered TS solution of 10 mM Tris, 0.25 M of Saccharose, 2 mM of dithiothreitol, HCl for a pH of 7.4 using a polytetrafluoroethylene-glass Potter at a rate of 1 g of tissue per 10 ml of TS. The homogenate was ultracentrifuged at 105,000 g for 90 minutes at 0° C. and aliquoits of the resulting surnageant were incubated at 0° C. for a time (t) with a constant concentration (T) of tritied dexamethasone in the presence of an increasing concentration (0 to 2500× 10^{-9}M) of either cold dexamethasone or cold test product. The concentration of tied tritied dexamethasone (B) was

measured for each incubate by the adsorption on carbon-dextran technique.

E. Estrogen receptor of uterus of mice

Immature female mice 18 to 21 days old were killed and the uterus were removed and homogenized at 0° C. with a polytetrafluoroethylene-glass Potter in a buffered TS solution consisting of 10 mM Tris, 0.25 M Saccharose, HCl for a pH of 7.4 at a rate of 1 g of tissue per 25 ml of TS. The homogenate was then ultracentrifuged at 105,000 g for 90 minutes at 0° C. and aliquoits of the resulting surnageant were incubated at 0° C. for a time (t) with a constant concentration (T) of tritied estradiol in the presence of increasing concentrations (0 to 1000×10^{-9}M) of either cold estradiol or cold test compound. The concentration of tied tritied estradiol (B) was measured for each incubate by the technique of adsorption on carbon-dextran.

The calculation of the relative affinity of concentration (ARL) was identical for all of the above receptor tests. One traced the following two curves: the percentage of tied tritied hormone B/T as a function of the logarithm of the cold hormone concentration and B/T as a function of the logarithm of the concentration of the cold test product. One determined the line of the equation.

$$I_{50} = \frac{\frac{B}{T}\text{ max.} + \frac{B}{T}\text{ min.}}{2}$$

B/T max. is the percentage of tied tritied hormone for an incubation of the tritied hormone at concentration T

B/T min. is the percentage of tied tritied hormone for an incubation of the tritied hormone at a concentration (T) in the presence of a large excess of cold hormone (2500×10^{-9}M).

The intersection of the I_{50} line and the curves permits one to determine the concentrations of the cold hormone of the reference (CH) and the cold test compound (CX) which inhibit by 50% the tieing of tritied hormone with the receptor. The relative affinity of tieing (ARL) of the test product was determined by the equation:

$$ARL = 100 \times \frac{CH}{CX}$$

The results are reported in the following Tables.

CONCLUSION

The tested compounds and especially those of Examples 4,10,16,17 and 22 present a very remarkable affinity for glucocorticoid and progestogen receptors as well as a slight affinity for androgen receptors. On the contrary, the products do not have any activity for mineralcorticoid and estrogen receptors. These results lead to the conclusion that the products present an agonist or antagonistic activity to glucocorticoids, progestogens and androgens.

IL Anti-inflammatory Activity

The anti-inflammatory activity of the compound of Example 4 was determined by the classical granuloma test by a modification of the Meier et al test [Experientia, Vol. 6 (1950), p. 469] in which normal female Wistar rats weighing 100 to 110 g received an implantation of 2 pellets of cotton weighing 10 mg each under the thorax skin. The subcutaneous treatment which began immediately after the implantation for 2 days was 2 injections per day. 16 hours after the last injection, the animals were killed and the pellets together with the granuloma tissue formed were weighed in the fresh state and after 16 hours at 60° C. The weight of the granuloma was obtained by subtracting the initial weight of the cotton. The thymus was also removed and weighed to determine the thymolytic activity of the test product.

At a subcutaneous dose of 50 mg/kg, the product of Example 4 did not show any glucocorticoidal anti-inflammatory activity or thymolytic activity.

III. Antiglucocorticoidal Activity

The test used was that of Daune et al [Molecular Pharmacology, Vol. 13 (1977), p. 948-955] entitled "The relationship between glucocorticoid structure and effects upon thymocytes" for mice thymocytes. The thymocytes of surrenalectomized rats were incubated at 37° C. for 3 hours in a nutritive medium containing 5×10^{-8}M of dexamethasone in the presence or absence of the test compound at different concentrations. Tritied uridine was added and incubation was continued for one hour. The incubates were cooled and treated with a 5% trifluoroacetic acid solution and the mixture was filtered with Whatman GF/A paper. The filter was washed 3 times with a 5% trifluoroacetic acid solution and retained radioactivity on the filter was determined. Glucocorticoids and especially dexamethasone provoked a lessening of incorporation of tritied uridine and the tested compounds, especially those of Examples

Product of Example	Time of incubation at 0° C.														
	Mineralo corticoid			Androgen			Progestogen			Gluco-corticoid			Estrogen		
	2H	4H	24H	2H	4H	24H	2H	4H	24H	2H	4H	24H	2H	4H	24H
4	—	—	0	—	—	20	74	—	640	—	270	265	0	—	—
17	—	—	0	—	—	66	81	—	351	—	279	225	0	—	—
14	—	—	—	—	—	0	41	—	230	—	46	94	0	—	—
8	—	—	0	—	—	14,7	81	—	266	—	212	167	0	—	—
10	—	—	0	—	—	32	78	—	467	—	234	292	0	—	—
11	—	—	0	—	—	9,8	6,3	—	8,3	—	9	14	0	—	—
16	—	—	1,7	—	—	29	129	—	166	—	283	259	0	—	—
12	—	—	0	—	—	2,8	0,6	—	0,4	—	5,3	6,2	0	—	—
6	—	—	0,8	—	—	7,3	10	—	4,3	—	171	118	0	—	—
20	—	—	—	—	—	2,2	1,1	—	2,5	—	7,8	5	0	—	—
22	—	—	0,3	—	—	8	175	—	843	—	178	221	0	—	—
29	—	—	0	—	—	4,6	15,2	—	38	—	79	104	0	—	—

4,6,8,10,11,14,16,20 and 22. opposed this effect as can be seen from the following Table.

Product of Example	$5 \cdot 10^{-8}$ Dexamethasone + Product tested	% of inhibition of effect of Dexamethasone
4	10^{-6}M	30
	10^{-7}M	70
	10^{-6}M	90
14	10^{-8}M	18
	10^{-7}M	57
	10^{-6}M	*
8	10^{-8}M	22
	10^{-7}M	53
	10^{-6}M	*
10	10^{-8}M	57
	10^{-7}M	83
	10^{-6}M	*
11	10^{-8}M	14
	10^{-7}M	34
	10^{-6}M	75
16	10^{-8}M	28
	10^{-7}M	60
	10^{-6}M	99
6	10^{-8}M	5
	10^{-7}M	15
	10^{-6}M	83
20	10^{-8}M	4
	10^{-7}M	21
	10^{-6}M	50
22	10^{-8}M	16
	10^{-7}M	69
	10^{-6}M	*

*A dose of 10^{-6}M inhibited totally the effect of dexamethasone

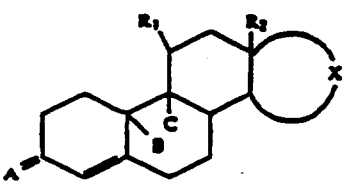
CONCLUSION

The products of the invention used alone do not provoke any effect of the glucocorticoid type and the tested products present a very remarkable antiglucocorticoid activity and are devoid of any glucocorticoid activity.

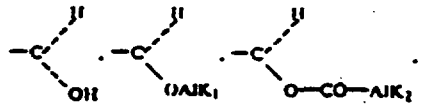
Various modifications of the products and methods of the invention may be made without departing from the spirit or scope thereof and it is to be understood that the invention is intended to be limited only as defined in the appended claims.

What we claim is:

1. A compound selected form the group consisting of 19-nor steroids and 19-nor-D-homo-steroids of the formula



wherein R_1 is an organic raffical of 1 to 18 carbon atoms containing at least one atom selected from the group consisting of nitrogen, phosphorous and silicon with the atom immediately adjacent to the 11-carbon atom being carbon, R_2 is a hydrocarbon of 1 to 8 carbon atoms, X is selected from the group consisting of a pentagonal ring and a hexagonal ring optionally substituted and optionally containing a double bond, B and C together form a double bond or an epoxy group, the C=A group at position 3 is selected from the group consisting of C=O, ketal,

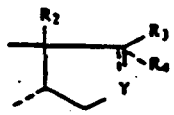


—C=NOH, —C=NOAlK$_3$ and =CH$_2$, AlK$_1$, AlK$_2$ and AlK$_3$ are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and their non-toxic, pharmaceutically acceptable acid addition salts.

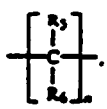
2. A compound of claim 1 wherein B and C form a double bond.

3. A compound of claim 1 or 2 wherein R_2 is methyl.

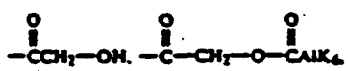
4. A compound of claim 1, 2 or 3 wherein X and the carbons to which it is attached form the ring of the formula

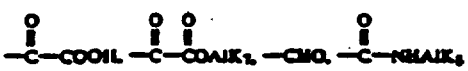


wherein R_2 has the above definition, the dotted line in the 16,17-position is an optional double bond, Y is the group

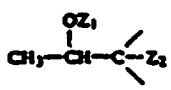


n is 1 or 2, R_5 is selected from the group consisting of hydrogen of 1 to 8 carbon atoms, alkenyl and alkynyl of 2 to 8 carbon atoms, aryl of 6 to 14 carbon atoms and aralkyl of 7 to 15 carbon atoms, R_6 may be the same as R_5 and may be selected from the same group of members are R_5 or —OH, R_3 and R_4 are individually selected from the group consisting of hydrogen, —OH, —OAlK$_4$, —OCOAlK$_5$, alkenyl and alkynyl of 2 to 8 carbon atoms,





and —CN wherein AlK$_4$, AlK$_5$ and AlK$_8$ are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms, AlK$_6$ is selected from the group consisting of optionally substituted alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and AlK$_7$ is alkyl of 1 to 8 carbon atoms and R_3 and R_4 form the group



and Z_1 is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms and acyl of an organic carboxylic acid of 1 to 8 carbon atoms and Z_2 is alkyl of 1 to 8 carbon atoms.

5. A compound of claim 4 wherein the D ring is saturated. R_5 and R_6 are hydrogen and n is 1.

6. A compound of claim 1 wherein the C=A group is C=O.

7. A compound of claim 1 wherein R_1 is a hydrocarbon of 1 to 18 carbon atoms containing at least one nitrogen atom.

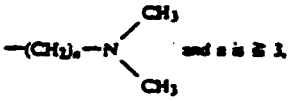
8. A compound of claim 7 wherein R_1 is a primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of nitrogen, sulfur and oxygen at least one being nitrogen or substituted with a heterocycle containing at least one nitrogen atom.

9. A compound of claim 7 wherein R_1 is heterocycle containing at least one nitrogen atom optionally substituted with an alkyl of 1 to 8 carbon atoms.

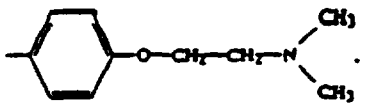
10. A compound of claim 7 wherein R_1 is aryl or aralkyl containing the group

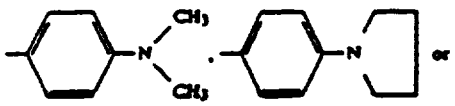
wherein R_7 and R_8 are alkyl of 1 to 8 carbon atoms or primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of nitrogen, sulfur and oxygen of which at least one is nitrogen or substituted with a heterocycle containing at least one nitrogen atom.

11. A compound of claim 10 wherein R_1 is selected from the group consisting of 2-pyridyl, 3-pyridyl, 4-pyridyl,

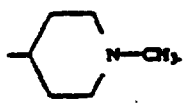


and a is ≧ 3,





or

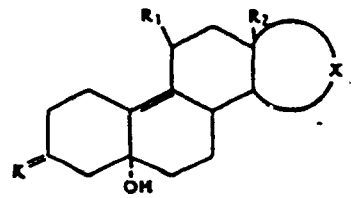


12. A compound of claim 1 wherein R_1 contains an oxidized nitrogen atom.

13. A compound of claim 1 selected from the group consisting of 11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-$\Delta^{4,9}$-pregnadiene-20-yne-17β-ol-3-one, N-oxide of 9α,10α-epoxy-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^4-pregnene-20-yne-17β-ol-3-one, 11β-[4-(N,N-dimethylamino)phenyl]-17α-(prop-2-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one, N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-

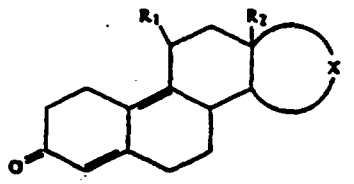
estradiene-17β-ol-3-one and their non-toxic, pharmaceutically acceptable acid addition salts.

14. A process for the preparation of a compound of claim 1 comprising reacting a compound of the formula



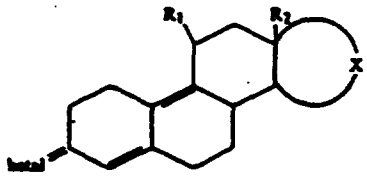
II

wherein K is a ketone blocked in the form of a ketal, thioketal, oxime or methyloxime and R_1, R_2 and X have the above definitions with a dehydration agent capable of freeing the ketone group to form a compound of the formula



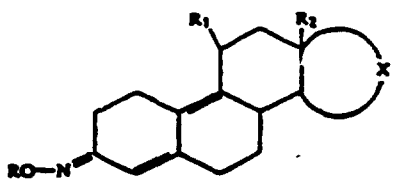
I_A

and either reacting the latter with a ketalization agent to obtain a compound of the formula



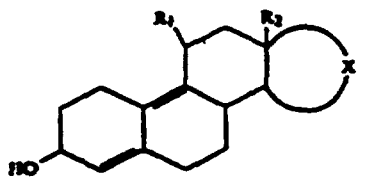
I_B

or reacting the compound of formula I_A' with NH_2OH or NH_2OAlK_3 wherein AlK_3 has the above definition to obtain a compound of the formula



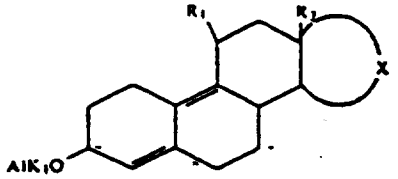
I_C

wherein R is hydrogen or AlK_3 or reacting a compound of formula I_A' with a reducing agent capable of selectively reducing the 3-keto group to obtain a compound of the formula

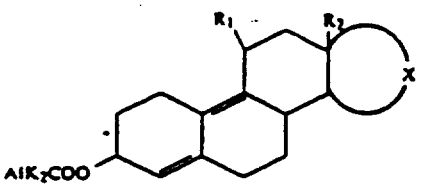


I_D

and reacting the latter with an etherification agent capable of introducing AlK_1 to obtain a compound of the formula

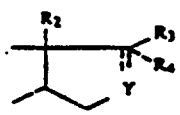


or reacting the compound of formula $I_{D'}$ with an esterification agent capable of introducing $COAlK_2$ to obtain a compound of the formula

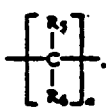


or transforming the compound of formula $I_{A'}$ by known methods to a compound wherein the C=A group is CH_2— and optionally reacting a compound of formula $I_{A'}$, $I_{B'}$, $I_{C'}$, $I_{D'}$, $I_{E'}$ or $I_{F'}$ with an acid to form the corresponding acid addition salt or with an oxidation agent to obtain when R_1 is a radical containing a nitrogen atom a compound having in the 11β-position a radical wherein the nitrogen atom is in the oxide form and B and C optionally form an epoxide bridge or when R_1 does not contain a nitrogen atom, a compound where B and C form an epoxide bridge and when the compound contains the nitrogen oxide and the B and C group form an epoxide bridge, selectively reducing the oxidized nitrogen atom in R_1 and optionally reacting the latter with an acid to form the acid addition salt.

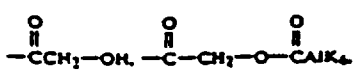
15. A process of claim 16 wherein X and the carbons to which it is attached form the ring of the formula



wherein R_2 has the above definition, the dotted line in the 16,17-position is an optional double bond, Y is the group



n is 1 or 2, R_5 is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms, alkenyl and alkynyl of 2 to 8 carbon atoms, aryl of 6 to 14 carbon atoms and aralkyl of 7 to 15 carbon atoms, R_6 may be the same as R_5 and may be selected from the same group of members as R_5 or —OH, R_3 and R_4 are individually selected from the group consisting of hydrogen, —OH, —$OAlK_4$, —$OCOAlK_5$, alkenyl and alkynyl of 2 to 8 carbon atoms,



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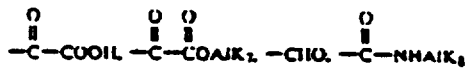
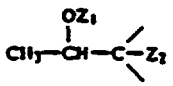
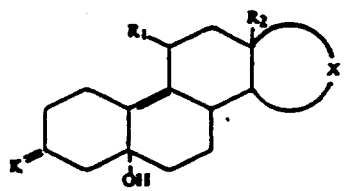


and —CN wherein AlK_4, AlK_5 and AlK_8 are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms, AlK_6 is selected from the group consisting of optionally substituted alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and AlK_7 is alkyl of 1 to 8 carbons atoms and R_3 and R_4 form the group

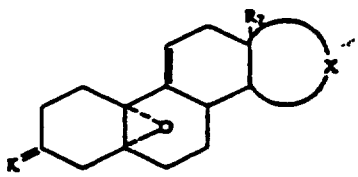


and Z_1 is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms and acyl of an organic carboxylic acid of 1 to 8 carbon atoms and Z_2 is alkyl of 1 to 8 carbon atoms.

16. A process for the preparation of a compound of the formula

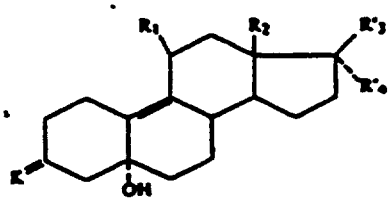


wherein R_1, R_2 and X have the definition of claim 1 and K is selected from the group consisting of ketal, thioketal, oxime and methyloxime wherein a compound of the formula



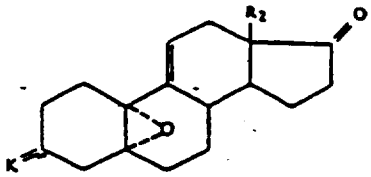
is reacted with a compound selected from the group consisting of $LiCu(R_1)_2$, LiR_1 and R_1MgHal wherein R_1 has the above definition and Hal is a halogen in the presence of a cuprous halide.

17. A process for the preparation of a compound of the formula



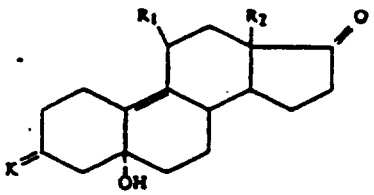
wherein R_1, R_2 and K have the above definitions, R_3' is selected from the group consisting of —OH and OR_c, R_c is the residue AlK_4 of an ether group or $COAlK_5$ of an ester group, AlK_4 and AlK_5 having the above definitions, and R_4' is hydrogen or alkenyl or alkynyl of 2 to

8 carbon atoms comprising reacting a compound of the formula



IV

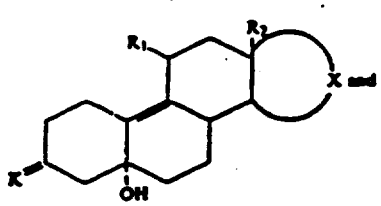
with a compound selected from the group consisting of $LiCu(R_1)_2$, R_1Li and R_1Mg Hal wherein R_1 and Hal have the above definitions in the presence of a cuprous halide to obtain a compound of the formula

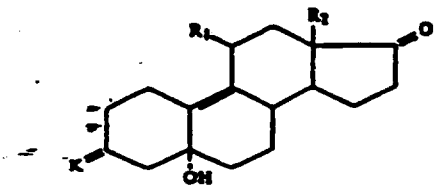


V

and either reducing the latter to obtain the corresponding 17-ol compound or with an appropriate magnesium to obtain the corresponding 17α-substituted-17β-ol steroid or with an organometallic derivative such as a lithium or potassium derivative to obtain the corresponding 17α-substituted-17β-ol steroid or with a cyanuration agent to obtain the corresponding 17α-ol-17β-cyano steroid, protecting the hydroxy group and reacting the latter with an organometallic compound as discussed above to obtain the corresponding 17α-substituted-17β-ol steroid and in the case of one of the compounds obtained is 17-hydroxylated, reacting it with an etherification agent or esterification agent and in the case when one of the compounds contains a 17 substituent with a triple bond reacting the latter with a reducing agent to obtain the corresponding ethylenic derivative.

18. A compound selected from the group consisting of





wherein R_1, R_2 and X have the definition of claim 1 and K is selected from the group consisting of ketal, thioketal, oxime and methyloxime.

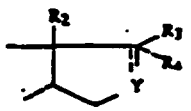
19. A compound of claim 18 selected from the group consisting of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-trimethylsilylphenyl]-17α-(prop-1-ynyl)-Δ⁹-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-(4-pyridyl)-17α-(prop-1-ynyl)-Δ⁹-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-Δ⁹-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ⁹-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-Δ⁹-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ⁹-pregnene-20-yne-5α,17β-diol and 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-Δ⁹-estrene-5α,17β-diol, 3,3-/1,2-ethane dilyl-bisoxy/-5α,10α-epoxy-17α-(prop-1-ynyl)Δ⁹⁽¹¹⁾-estrene-17β-ol.

20. An antiglucocorticoid composition comprising an antiglucocorticoidally effective amount of at least one compound of claim 1 and an inert carrier.

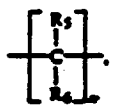
21. A composition of claim 20 wherein B and C form a double bond.

22. A composition of claim 20 wherein R_2 is methyl.

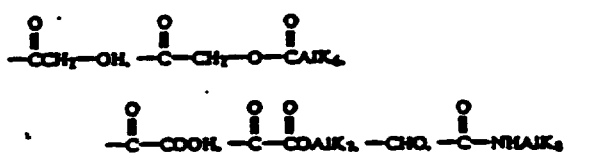
23. A composition of claim 20 wherein X and the carbons to which it is attached form the ring of the formula



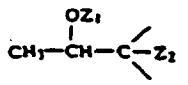
wherein R_2 has the above definition, the dotted line in the 16,17-position is an optional double bond, Y is the group



n is 1 or 2, R_5 is selected from the group consisting of hydrogen of 1 to 8 carbon atoms, alkenyl and alkynyl of 2 to 8 carbon atoms, aryl of 6 to 14 carbon atoms and aralkyl of 7 to 15 carbon atoms, R_6 may be the same as R_5 and may be selected from the same group of members as R_5 or —OH, R_3 and R_4 are individually selected from the group consisting of hydrogen, —OH, —$OAlK_4$, —$OCOAlK_5$, alkenyl and alkynyl of 2 to 8 carbon atoms,



and —CN wherein AlK_4, AlK_5 and AlK_8 are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms, AlK_6 is selected from the group consisting of optionally substituted alkyl of 1 to 8 carbon atoms and aralkyl to 7 to 15 carbon atoms and AlK_7 is alkyl of 1 to 8 carbon atoms and R_3 and R_4 form the group



and Z_1 is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms and acyl of an organic carboxylic acid of 1 to 8 carbon atoms and Z_2 is alkyl of 1 to 8 carbon atoms.

24. A composition of claim 23 wherein the D ring is saturated, R_5 and R_6 are hydrogen and n is 1.

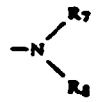
25. A composition of claim 20 wherein the C=A group is C=O.

26. A composition of claim 20 wherein R_1 is a hydrocarbon of 1 to 18 carbon atoms containing at least one nitrogen atom.

27. A composition of claim 26 wherein R_1 is a primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of nitrogen, sulfur and oxygen at least one being nitrogen or substituted with a heterocycle containing at least one nitrogen atom.

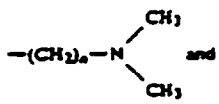
28. A composition of claim 26 wherein R_1 is heterocycle containing at least one nitrogen atom optionally substituted with an alkyl of 1 to 8 carbon atoms.

29. A composition of claim 26 wherein R_1 is aryl or aralkyl containing the group

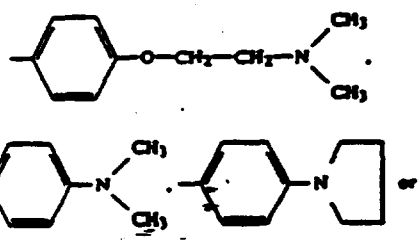


wherein R_7 and R_8 are alkyl of 1 to 8 carbon atoms or primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of nitrogen, sulfur and oxygen of which at least one is nitrogen or substituted with a heterocycle containing at least one nitrogen atom.

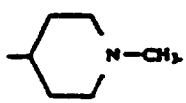
30. A composition of claim 29 wherein R_1 is selected from the group consisting of 2-pyridyl, 3-pyridyl, 4-pyridyl,



and n is 2 or 3,



or



31. A composition of claim 20 wherein R_1 contains an oxidized nitrogen atom.

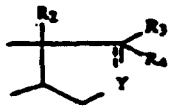
32. The composition of claim 20 wherein the active compound is selected from the group consisting of 11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one, 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one, N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-Δ4,9-pregnadiene-20-yne-17β-ol-3-one, N-oxide of 9α,10α-epoxy-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ4-pregnene-20-yne-17β-ol-3-one, 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-Δ4,9-estradiene-17β-ol-3-one, N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one and their non-toxic, pharmaceutically acceptable acid addition salts.

33. A method of inducing antiglucocorticoid activity in warm-blooded animals comprising administering to warm-blooded animals an antiglucocorticoidally effective amount of at least one compound of claim 1.

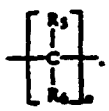
34. A method of claim 33 wherein B and C form a double bond.

35. A method of claim 33 wherein R_2 is methyl.

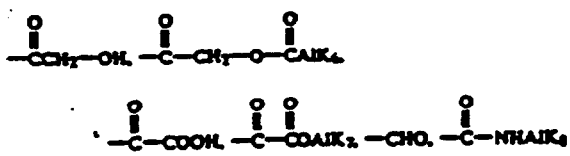
36. A method of claim 33 wherein X and the carbons to which it is attached form the ring of the formula



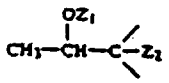
wherein R_2 has the above definition, the dotted line in the 16,17-position is an optional double bond, Y is the group



n is 1 or 2, R_5 is selected from the group consisting of hydrogen of 1 to 8 carbon atoms, alkenyl and alkynyl of 2 to 8 carbon atoms, aryl of 6 to 14 carbon atoms and aralkyl of 7 to 15 carbon atoms, R_6 may be the same as R_5 and may be selected from the same group of members as R_5 or —OH, R_3 and R_4 are individually selected from the group consisting of hydrogen, —OH, —$OAlK_4$, —$OCOAlK_5$, alkenyl and alkynyl of 2 to 8 carbon atoms,



and —CN wherein AlK_4, AlK_5 and AlK_8 are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms, AlK_6 is selected from the group consisting of optionally substituted alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and AlK_7 is alkyl of 1 to 8 carbon atoms and R_3 and R_4 form the group



and Z_1 is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms and acyl of an organic carboxylic acid of 1 to 8 carbon atoms and Z_2 is alkyl of 1 to 8 carbon atoms.

37. A method of claim 36 wherein the D ring is saturated, R_5 and R_6 are hydrogen and n is 1.

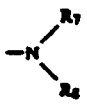
38. A method of claim 33 wherein the C=A group is C=O.

39. A method of claim 33 wherein R_1 is a hydrocarbon of 1 to 18 carbon atoms containing at least one nitrogen atom.

40. A method of claim 39 wherein R_1 is a primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of nitrogen, sulfur and oxygen at least one being nitrogen or substituted with a heterocycle containing at least one nitrogen atom.

41. A method of claim 39 wherein R_1 is heterocycle containing at least one nitrogen atom optionally substituted with an alkyl of 1 to 8 carbon atoms.

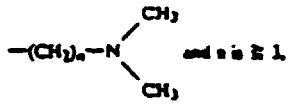
42. A method of claim 39 wherein R_1 is acyl or aralkyl containing the group



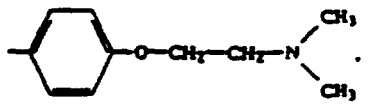
wherein R_7 and R_8 are alkyl of 1 to 8 carbon atoms or primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of nitrogen, sulfur and oxygen of which at

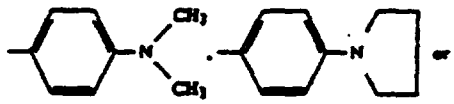
least one is nitrogen, or substituted with a heterocycle containing at least one nitrogen atom.

43. A method of claim 42 wherein R_1 is selected from the group consisting of 2-pyridyl, 3-pyridyl, 4-pyridyl,

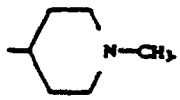


and n is ≥ 1,





or



44. A method of claim 33 wherein R_1 contains an oxidized nitrogen atom.

45. A compound of claim 1 selected from the group consisting of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one and its non-toxic, pharmaceutically-acceptable acid addition salts.

46. A method of claim 33 wherein the compound is selected from the group consisting of 11β-[4,-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one and its non-toxic, pharmaceutically acceptable acid addition salts.

* * * * *

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

US Patent No.: 4,447,424

APPEARS THIS WAY
ON ORIGINAL

The Population Council

Center for
Medical Research

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New York, New York 10021
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To Whom It May Concern:

The undersigned declares that Patent No. 4,447,424 covers the formulation, composition, and/or method of use of Mifepristone [trade name undertermined]. This product is the subject of this application for which approval is being sought.

Signed on: October 3, 1995

for The Population Council

C. Wayne Bardin, MD

C. Wayne Bardin, M.D.
Vice President

APPEARS THIS WAY
ON ORIGINAL

United States Patent [19]
Teutsch et al.

[11] 4,447,424
[45] May 8, 1984

[54] STEROID DERIVATIVES

[75] Inventors: Jean G. Teutsch, Pantin; Germain Costerousse, Saint-Maurice; Daniel Philibert, La Varenne Saint Hilaire; Roger Deraedt, Pavillons sous Bois, all of France

[73] Assignee: Roussel Uclaf, Paris, France

[21] Appl. No.: 386,967

[22] Filed: Jun. 10, 1982

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 338,077, Jan. 9, 1982, Pat. No. 4,386,085.

[30] Foreign Application Priority Data

Jan. 9, 1981 [FR] France 81 00272

[51] Int. Cl.³ A01N 45/00; A61K 31/56

[52] U.S. Cl. ..... 424/238; 424/241; 424/243; 260/239.55 R; 260/239.55 C; 260/239.5; 260/397.45; 260/397.1

[58] Field of Search 260/397.45, 239.5, 239.55; 424/243, 238, 241

[56] References Cited

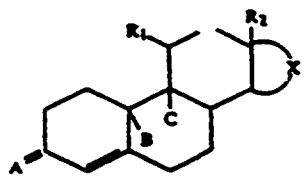
U.S. PATENT DOCUMENTS

4,197,296 4/1980 Phillipps et al. 260/397.45

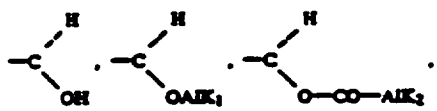
Primary Examiner—Elbert L. Roberts
Attorney, Agent, or Firm—Bierman, Bierman & Peroff, Muserlian

[57] ABSTRACT

Novel 19-nor steroids and 19-nor-D-homo-steroids of the formula



wherein R_1 is an organic radical of 1 to 18 carbon atoms containing at least one atom selected from the group consisting of nitrogen, phosphorous and silicon with the atom immediately adjacent to the 11-carbon atom being carbon, R_2 is a hydrocarbon of 1 to 8 carbon atoms, X is selected from the group consisting of a pentagonal ring and a hexagonal ring optionally substituted and optionally containing a double bond, B and C together form a double bond or an epoxy group, the C=A group at position 3 is selected from the group consisting of C—O, ketal, which may be open or closed



—C=NOH, —C—NOAlK$_3$ and C—CH$_2$, AlK$_1$, AlK$_2$ and AlK$_3$ are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and their non-toxic, pharmaceutically acceptable acid addition salts having anti-glucocorticoid activity and a process for their preparation.

36 Claims, No Drawings

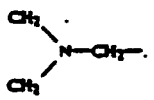
STEROID DERIVATIVES

PRIOR APPLICATION

This application is a continuation-in-part of copending, commonly assigned U.S. patent application Ser. No. 338,077 filed Jan. 9, 1982, now U.S. Pat. No. 4,386,085.

STATE OF THE ART

U.S. Pat. No. 4,233,296 describes steroids being substituted in the 11-position with substituents other than the present formula which require an organic substituent containing a nitrogen, phosphorous or silicon atom. U.S. Pat. No. 3,190,796 describes steroids having in a hydroxyl in the 11β-position. Schoenemann et al. European Journal of Medicine Chemistry, Chimica Therapeutica, Vol. 15, No. 4, (July, August 1980), p. 333-335) describes steroids substituted in the 11β-position with CH_2=, $-CH_2OH$ and



OBJECTS OF THE INVENTION

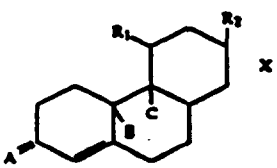
It is an object of the invention to provide the novel steroids of formula I and their non-toxic, pharmaceutically acceptable acid addition salts and a novel process and novel intermediates for their preparation.

It is another object of the invention to provide novel antiglucocorticoid compositions and to a novel method of inducing antiglucocorticoidal activity in warm-blooded animals.

These and other objects and advantages of the invention will become obvious from the following detailed description.

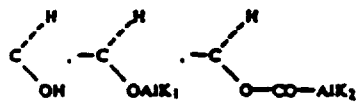
THE INVENTION

The novel steroids of the invention are selected from the group consisting of 19-nor steroids and 19-nor-D-homo-steroids of the formula



I

wherein R_1 is an organic radical of 1 to 18 carbon atoms containing at least one atom selected from the group consisting of nitrogen, phosphorous and silicon with the atom immediately adjacent to the 11-carbon atom being carbon, R_2 is a hydrocarbon of 1 to 8 carbon atoms, X is selected from the group consisting of a pentagonal ring and a hexagonal ring optionally substituted and optionally containing a double bond, B and C together form a double bond or an epoxy group, the C=A group at position 3 is selected from the group consisting of C=O ketal, which may be open or closed-

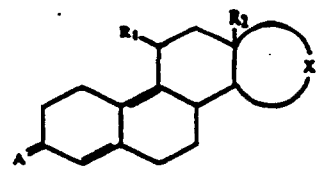


—C=NOH, —C=NOAlK$_3$ and C=CH_2, AlK$_1$, AlK$_2$ and AlK$_3$ are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and their non-toxic, pharmaceutically acceptable acid addition salts.

Preferably R_2 is a saturated alkyl of 1 to 4 carbon atoms such as methyl, ethyl, n-propyl or butyl and AlK$_1$, AlK$_2$ and AlK$_3$ are preferably methyl, ethyl, n-propyl, isopropyl or benzyl. X is preferably an optionally substituted remainder of a pentagonal ring.

Examples of suitable acids for the non-toxic, pharmaceutically acceptable acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and phosphoric acid and organic acids such as acetic acid, formic acid, propionic acid, benzoic acid, maleic acid, fumaric acid, succinic acid, tartaric acid, citric acid, oxalic acid, glyoxylic acid, aspartic acid, alkane sulfonic acids such as methane sulfonic acid and ethane sulfonic acid, aryl sulfonic acids such as benzene sulfonic acid and p-toluene sulfonic acid and arylcarboxylic acid.

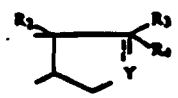
A preferred group of compounds are those of the formula



I'

wherein R_1, R_2, A and X have the above definitions and their non-toxic, pharmaceutically acceptable acid addition salts.

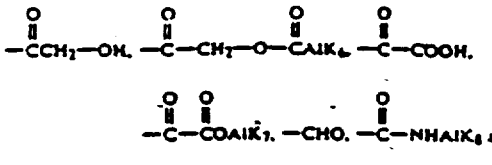
Preferred compounds of formula I' are those wherein R_2 is methyl, those wherein X is the remainder of the pentagonal ring



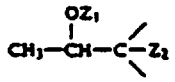
wherein R_2 has the above definition, the dotted line in the 16,17-position is an optional double bond, Y is the group

a is 1 or 2, R_5 is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms, alkenyl and alkynyl of 2 to 8 carbon atoms, aryl of 6 to 14 carbon atoms and aralkyl of 7 to 15 carbon atoms, R_6 may be the same as R_5 and may be selected from the same group of members as R_5 or —OH, R_3 and R_4 are individually selected from the group consisting of hydrogen, —OH,

—OAlK$_4$, —OCOAlK$_5$, alkenyl and alkynyl of 2 to 8 carbon atoms,



wherein AlK$_4$, AlK$_5$ and AlK$_8$ are selected from the group consisting of alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms, AlK$_6$ is selected from the group consisting of optionally substituted alkyl of 1 to 8 carbon atoms and aralkyl of 7 to 15 carbon atoms and AlK$_7$ is alkyl of 1 to 8 carbon atoms and R_3 and R_4 form the group



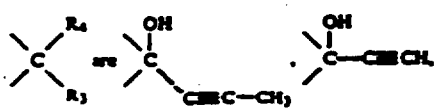
and Z_1 is selected from the group consisting of hydrogen, alkyl of 1 to 8 carbon atoms and acyl of an organic carboxylic acid of 1 to 8 carbon atoms and Z_2 is alkyl of 1 to 8 carbon atoms and those where R_5 is different from R_6.

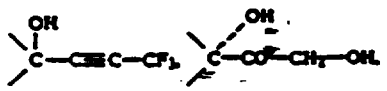
When R_5 or R_6 are alkyl, they are preferably methyl or ethyl and when they are alkenyl or alkynyl, they are vinyl, isopropenyl, allyl, ethynyl or propynyl. When R_5 and R_6 are aryl or aralkyl, they are phenyl or benzyl.

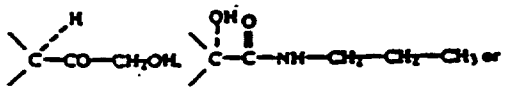
When R_3 or R_4 are OAlK$_4$ or

AlK$_4$ or AlK$_5$ are preferably methyl, ethyl, n-propyl, butyl, pentyl, hexyl or benzyl. When R_3 or R_4 are alkenyl or alkynyl, they are preferably vinyl, isopropenyl, allyl or 2-methylallyl or ethynyl or —C≡C—AlK$_9$ where AlK$_9$ is methyl, ethyl, propyl, isopropyl, isopropenyl, butyl, benzyl or CF_3—, AlK$_6$, AlK$_7$ or AlK$_8$ have preferably the same values as AlK$_4$ and AlK$_5$. The groups R_3 and R_4 are preferably different except where R_3 or R_4 each are hydrogen.

Among the preferred values of







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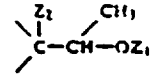


wherein Z_1 is hydrogen, alkyl of 1 to 8 carbon atoms or acyl of a hydrocarbon of 2 to 8 carbon atoms such as acetyloxy or benzoyl and Z_2 is alkyl of 1 to 8 carbon atoms such as methyl.

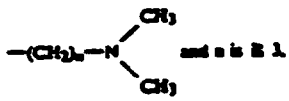
Other preferred compounds of formula I' are those wherein the D ring does not contain any ethylenic unsaturation, R_5 and R_6 are hydrogen, n is 1 and those compounds wherein =A is =O as well as those wherein R_1 is a hydrocarbon of 1 to 18 carbon atoms containing a nitrogen atom.

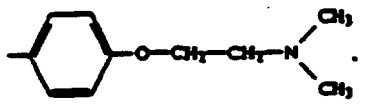
Especially preferred are the compounds of formula I' wherein R_1 is a primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of oxygen, nitrogen and sulfur at least one of which is nitrogen or is substituted with a nitrogen heterocycle. Examples of alkyl are methyl, ethyl, n-propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, hexyl and cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. Examples of heterocycle containing a nitrogen atom are 3-pyridyl, 4-pyridyl, 2-pyridyl, thiazolyl and piperidinyl.

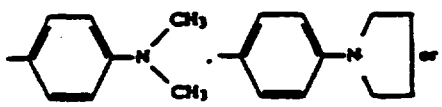
Equally preferred are compounds of formula I' wherein R_1 is a heterocycle containing at least one nitrogen atom optionally substituted with alkyl of 1 to 8 carbon atoms.

Other preferred compounds of formula I' are those wherein R_1 is aryl or aralkyl substituted with a group

wherein R_7 and R_8 are alkyl of 1 to 8 carbon atoms or primary, secondary or tertiary alkyl of 1 to 8 carbon atoms containing at least one heteroatom of the group consisting of nitrogen, sulfur or oxygen of which at least one is nitrogen or a heterocycle containing at least one nitrogen atom. Examples of alkyl are those mentioned above as preferred and aryl or aralkyl are preferably phenyl or benzyl and the preferred heterocycles are those mentioned above. Especially preferred are those wherein R_1 is 2-pyridyl, 3-pyridyl, 4-pyridyl







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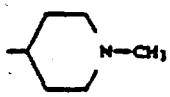
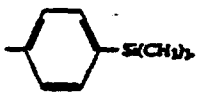
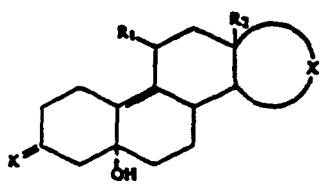


and especially those wherein R_1 is



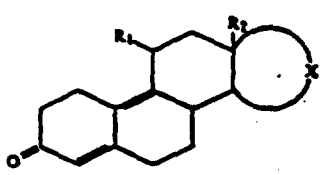
Among other preferred compounds are those wherein R_1 is a nitrogen oxide as well as those wherein B and C form an epoxy. Especially preferred compounds are those of Examples 1,3,4,8,10,11,12,14,16,17,20,22,28 and 29.

The novel process of the invention for the preparation of compounds of formula I' comprises reacting a compound of the formula



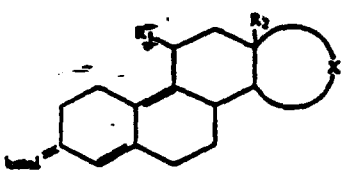
II

wherein K is a ketone blocked in the form of a ketal, thioketal, oxime or methyloxime and R_1, R_2 and X have the above definitions with a dehydration agent capable of freeing the ketone group to form a compound of the formula



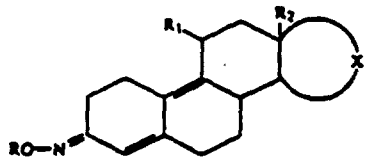
I_A'

and either reacting the latter with a ketalization agent to obtain a compound of the formula



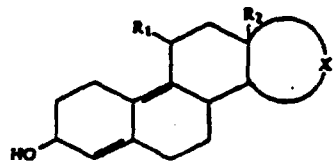
I_B'

or reacting the compound of formula I_A' with NH_2OH or NH_2OAlK_3 wherein AlK_3 has the above definition to obtain a compound of the formula



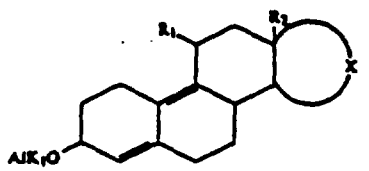
I_C'

wherein R is hydrogen or AlK_3 or reacting a compound of formula I_A' with a reducing agent capable of selectively reducing the 3-keto group to obtain a compound of the formula



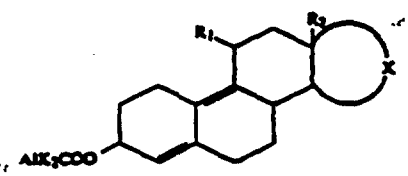
I_D'

and reacting the latter with an etherification agent capable of introducing AlK_1 to obtain a compound of the formula



I_E'

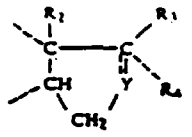
or reacting the compound of formula I_D' with an esterification agent capable of introducing $COAlK_2$ to obtain a compound of the formula



I_F'

or transforming the compound of formula I_A' by known methods to a compound wherein $C_{5-6}A$ is CH_2 and reacting a compound of formula I_A', I_B', I_C', I_D', I_E' or I_F' with an acid to form the corresponding acid addition salt or with an oxidation agent to obtain when R_1 is a radical containing a nitrogen atom a compound having in the 11β-position a radical wherein the nitrogen atom is in the oxide form and B and C optionally form an epoxide bridge or when R_1 does not contain a nitrogen atom, a compound where B and C form an epoxide bridge and when the compound contains the nitrogen oxide and the B and C group form an epoxide bridge, selectively reducing the oxidized nitrogen atom in R_1 and optionally reacting the latter with an acid to form the acid addition salt.

The process of the invention is particularly useful for forming products of formula I' wherein X form a pentagonal ring of the formula



wherein R_2, R_3, R_4, Y and the dotted line in the 16,17-position have the above definition.

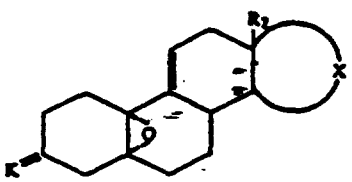
In a preferred mode of the process of the invention, the dehydration agent capable of freeing the ketone group is a sulfonic acid resin in the acid form such as a commercial sulfonic acid resin based on polystyrene or a styrene-divinylbenzene polymer but equally useful are inorganic acids such as sulfuric acid or hydrochloric acid in a lower alkanol or perchloric acid in acetic acid or a sulfonic acid such as p-toluene sulfonic acid.

The ketalization agent is preferably an alcohol or a dialcohol in the presence of an organic acid such as oxalic acid or p-toluene sulfonic acid. The agent for reducing the ketone group is preferably an alkali metal hydride as discussed by Walkis [Chemical Society Review, Vol. 5, No. 1 (1976), p. 23]. The etherification agent is preferably an alkyl halide in the presence of a base and the esterification agent is preferably a carboxylic acid derivative such as the acid anhydride or acid chloride in the presence of a base such as pyridine.

It goes without saying that when one of R_3 or R_4 in the compounds of formula I' obtained above is —OH, the compounds of formula I' may be reacted with an etherification agent or an esterification agent which is one of those discussed above. When R_3 or R_4 is a 17-acyloxy, the compound may be optionally saponified with a saponification agent such as a base like sodium hydroxide, potassium hydroxide, potassium amide or potassium tert.-butylate and the reaction is preferably effected in a lower alkanol such as ethanol or methanol but equally useful is lithium acetylide in ethylenediamine.

The oxidation agent is preferably a peracid such as m-chloroperbenzoic acid, peracetic acid or perphthalic acid or hydrogen peroxide alone or in the presence of hexachloroacetone or hexafluoroacetone. When it is desired to obtain a compound in which the nitrogen atom of R_1 is oxidized, one uses an equivalent of the oxidation agent and when it is desired to obtain a compound in which B and C form an epoxide bridge, two equivalents of agent are used. The selective reducing agent for the N-oxide is preferably triphenylphosphine and operating for example with acetic acid.

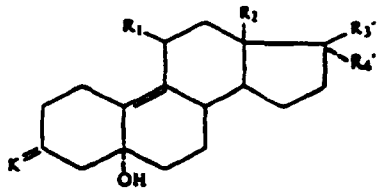
Another object of the invention is a process for the preparation of the compounds of formula II wherein a compound of the formula



III

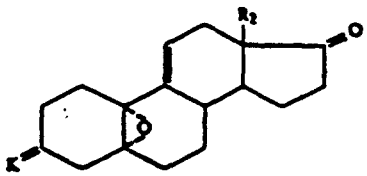
is reacted with a compound selected from the group consisting of $LiCu(R_1)_2$, LiR_1 and R_1Mg Hal wherein R_1 has the above definition and Hal is halogen in the presence of a cuprous halide. In a preferred mode of the said process, the reaction is effected at room temperature and the reactant is R_1Mg Hal in the presence of a cuprous salt.

Another object of the invention is a process for the preparation of a compound of the formula



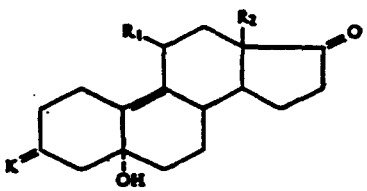
II'

wherein R_1, R_2 and K have the above definitions, R_3' is selected from the group consisting of —OH and OR_c, R_c is the residue AlK_4 of an ether group or $COAlK_5$ of an ester group and R_4' is hydrogen or alkenyl or alkynyl of 2 to 8 carbon atoms comprising reacting a compound of the formula



IV

with a compound selected from the group consisting of $LiCu(R_1)_2$, R_1Li and R_1Mg Hal in the presence of a cuprous halide to obtain a compound of the formula



V

and either reducing the latter to obtain the corresponding 17-ol compound or with an appropriate magnesium to obtain the corresponding 17α-substituted-17β-ol steroid or with an organometallic derivative such as a lithium or potassium derivative to obtain the corresponding 17α-substituted-17β-ol steroid or with a cyanuration agent to obtain the corresponding 17α-ol-17β-cyano steroid, protecting the hydroxy group and reacting the latter with an organometallic compound as discussed above to obtain the corresponding 17α-substituted-17β-ol steroid and in the case of one of the compounds obtained is 17-hydroxylated, reacting it with an etherification agent or esterification agent and in the case when one of the compounds contains a 17 substituent with a triple bond reacting the latter with a reducing agent to obtain the corresponding ethylenic derivative.

In a preferred mode of the latter process, the reaction of the compound of formula IV with a compound of the group consisting of RLi, $LiCu(R_1)_2$ or R_1Mg Hal is effected under the previously described conditions. The different reactants for reaction with the compounds of formula V are known in steroid chemistry and are illustrated in the specific examples.

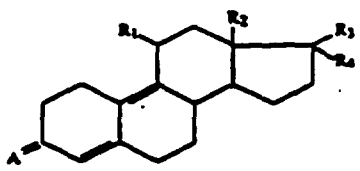
The novel intermediates of the invention are the compounds of formula II and V. Particularly preferred

compounds of the invention are 3,3-[1,2-ethanediyl bisoxy]-11β-[4-trimethylsilyl-phenyl]-17α-(prop-1-ynyl)-Δ⁹-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-(4-pyridyl)-17α-(prop-1-ynyl)-Δ⁹-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-Δ⁹-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ⁹-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-Δ⁹-estrene-5α,17β-diol, 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ⁹-pregnene-20-yne-5α,17β-diol and 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-Δ⁹-estrene-5α,17β-diol.

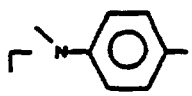
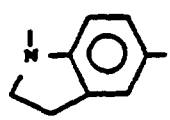
The compounds of formula III and especially of formula IV used to prepare the compounds of formula II or V are generally known compounds which can be prepared by reacting the corresponding $\Delta^{5(10),9(11)}$ steroids with an epoxidation agent selective for the 5(10) double bond, for example with hydrogen peroxide in the presence of hexachloroacetone or hexafluoroacetone as described in French Pat. No. 2,421,486. The new compound, 3,3-[1,2-ethanediyl-bisoxy]-17α-(prop-1-ynyl)-5α,10α-epoxy-$\Delta^{9(11)}$-estrene-17β-ol is prepared in the Example.

The following compounds are compounds falling within the scope of the invention:

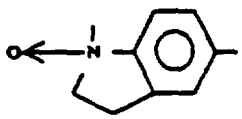
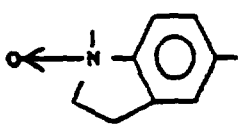
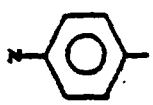
(A) compounds of the formula



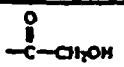
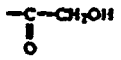
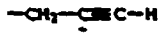
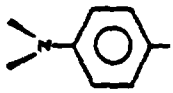
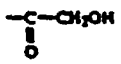
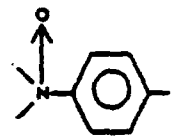
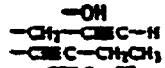
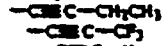
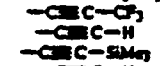
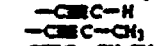
wherein the A, R_1, R_2, R_3 and R_4 substitutes are indicated in Table I.

A	R_1	R_2	R_3	R_4
O		CH_3	OH	$-C\equiv C-H$
"	"	"	"	$-C\equiv C-CF_3$
"	"	"	"	$-C\equiv C-CH_2CH_3$
"	"	"	"	$-CH_2-C\equiv C-H$
"	"	"	"	$-C\equiv C-Si(CH_3)_3$
"	"	"	$-C\equiv C-H$	OH
"	"	"	$-C\equiv C-Si(CH_3)_3$	OH
"	"	CH_2CH_3	OH	$-C\equiv C-H$
"	"	"	OH	$-C\equiv C-CH_3$
"	"	"	OH	$-CH_2-C\equiv C-H$
"	"	CH_3	$-C(=O)-CH_2OH$	H
"	"	"	"	OH
HO—N=(E)	"	"	OH	$-C\equiv C-H$
"	"	"	"	$-C\equiv C-CH_3$
"	"	"	$-C\equiv C-H$	OH
"	"	"	OH	$-CH_2-C\equiv C-H$
HO—N=(Z)	"	"	OH	$-C\equiv C-H$
"	"	"	"	$-C\equiv C-CH_3$
"	"	"	"	$-CH_2-C\equiv C-H$
"	"	"	$-C\equiv C-H$	OH
O		"	OH	$-C\equiv C-H$
"	"	"	"	$-C\equiv C-CF_3$
"	"	"	"	$-CH_2-C\equiv C-H$
"	"	"	"	$-C\equiv C-CH_2CH_3$
"	"	"	"	$-C\equiv C-Cl$
"	"	"	"	$-C\equiv C-Si(CH_3)_3$
"	"	"	$-C\equiv C-H$	OH
"	"	"	$-C\equiv C-Si(CH_3)_3$	OH
"	"	CH_2CH_3	OH	$-C\equiv C-H$
"	"	"	"	$-C\equiv C-CH_3$
"	"	"	"	$-CH_2-C\equiv C-H$
"	"	CH_3	$-C(=O)-CH_2OH$	H
"	"	"	"	OH

-continued

A	R_1	R_2	R_3	R_4
-	-	-	$-C(=O)-CH_3$	-H
HO—N=(E)	-	-	-OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-CH_2CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	-OH
-	-	-	$-C(=O)-CH_2OH$	H
HO—N=(Z)	-	-	-	-
-	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-CH_2CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	-OH
O		-	-	-
-	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CF_3$
-	-	-	-	$-C\equiv C-Cl$
-	-	-	-	$-C\equiv C-CH_2CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	-	$-C\equiv C-SiMe_3$
-	-	-	$-C(=O)-CH_2OH$	-H
HO—N=(E)		CH_3	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	-OH
HO—N=(Z)	-	-	-	-
-	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
O		-	-	$-C\equiv C-CH_2CH_3$
-	-	-	-	$-C\equiv C-CF_3$
-	-	-	$-C\equiv C-SiMe_3$	-OH
-	-	-	$-C(=O)-CH_2OH$	-H
-	-	-	-	-OH
-	-	-	$-C(=O)-CH_3$	-H
-	-	CH_2CH_3	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-Cl$
-	-	-	-	$-C\equiv C-CH_2-CH_3$
-	-	-	-	$-C\equiv C-SiMe_3$
-	-	-	-	$-CH_2-C\equiv C-H$

-continued

A	R_1	R_2	R_3	R_4
-	-	-		—H
HO—N=(E)	-	CH_3	—C≡C—H	—OH
-	-	-		—H
HO—N=(Z)	-	-	OH	
-		CH_3	—C≡C—H	—OH
-	-	-		—H
O		-	-	-
-	-	-	—C≡C—H	—OH
-	-	-	OH	
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-	-	
HO—N=(E)	-	-	OH	
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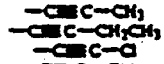
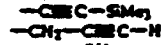
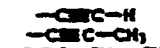
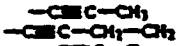
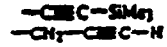
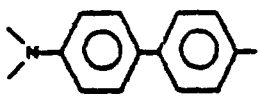
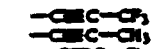
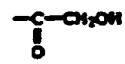
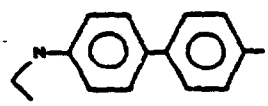
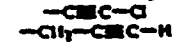
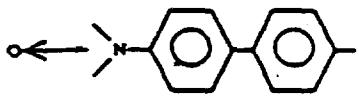
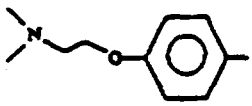
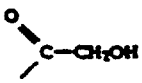
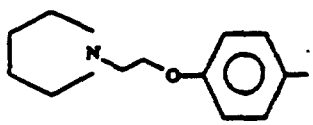
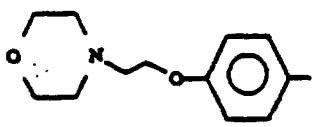
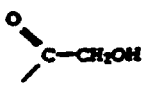
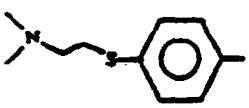
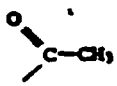
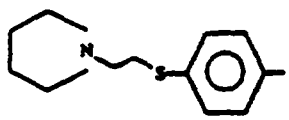
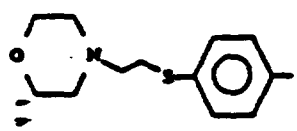
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-	—C≡C—H	—OH
HO—N=(Z)	-	-	OH	
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-	-	
O		-	OH	—C≡C—H
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-	-	
-	-	-	—C≡C—H	—OH
-	-	-		—H
-		-	-	-
-	-	-	OH	
-	-	-	-	
-	-	-	-	
-	-	-	-	

-continued

A	R_1	R_2	R_3	R_4
-	-	-	$-C\equiv C-H$	$-OH$
-		-	-	-
-		-	OH	$-C\equiv C-H$
-		-	-	$-C\equiv C-CF_3$
-		-	-	$-C\equiv C-CH_3$
-		-	-	$-CH_2-C\equiv C-H$
-		-	-	$-H$
-		-	-	$-C\equiv C-H$
-		-	-	$-CH_2-C\equiv C-H$
-		-	$-C\equiv C-H$	$-OH$
-		-		$-H$
-		-	-	-
-		-	$-C\equiv C-H$	$-OH$
-		-	$-OH$	$-C\equiv C-H$
-		-	-	$-C\equiv C-CH_3$
-		-	-	$-CH_2-C\equiv C-H$
-		-	$-OH$	$-C\equiv C-H$
-		-	-	$-C\equiv C-CH_3$
-		-	-	$-CH_2-C\equiv C-H$
-		-	$-C\equiv C-H$	$-OH$
-		-		$-H$
-		-	-	-
-		-	$-C\equiv C-H$	OH
-		-	OH	$-C\equiv C-CF_3$
-		-	OH	$-C\equiv C-H$
-		-	-	$-CH_2-CH=CH_2$
-		-	-	$CH_2-C\equiv C-H$
-		-	-	$-CH_2$
-		-		$-CH_3$
-		-	OH	$-CH_2-CN$
HO—N=(E)		-	OH	$-C\equiv C-H$
-		-	-	$-C\equiv C-CH_3$
-		-	-	$-C\equiv C-CH_2CH_3$
-		-	-	$-C\equiv C-Cl$

-continued

A	R_1	R_2	R_3	R_4
				$-CH_2-C\equiv C-H$
			$-C\equiv C-H$	$-OH$
				$-H$
			$-C(=O)-CH_2OH$	
HO—N=(Z)				
			$-C\equiv C-H$	$-OH$
			OH	$-C\equiv C-H$
				$-C\equiv C-CH_3$
				$-C\equiv C-CH_2-CH_3$
				$-C\equiv C-Cl$
				$-CH_2-C\equiv C-H$
O		CH_2CH_3		$-C\equiv C-H$
				$-C\equiv C-CH_3$
				$-CH_2-C\equiv C-H$
				$-CH_2-CH=CH_2$
				$-CH_3$
			$-C(=O)-CH_3$	
				$-H$
			$-C(=O)-CH_2OH$	
			$-C\equiv C-H$	$-OH$
		CH_3	OH	$-C\equiv C-H$
				
				$-C\equiv C-CH_3$
				$-C\equiv C-Cl$
				$-C\equiv C-CH_2CH_3$
				$-CH_2-C\equiv C-H$
				$-CH_2-CH=CH_2$
			$-C\equiv C-H$	$-OH$
				$-H$
			$-C(=O)-CH_2OH$	
				$-CH_3$
			$-C(=O)-CH_3$	
				$-H$
				
				$-CH_3$
			O	$-H$
			$-C(=O)-CH_2OH$	
			$-C\equiv C-H$	$-OH$
			OH	$-C\equiv C-H$
				$-C\equiv C-CH_3$
				$-C\equiv C-Cl$
				$-C\equiv C-CH_2CH_3$
				$-CH_2-C\equiv C-H$

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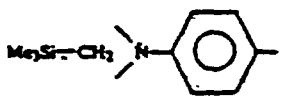
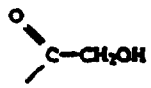
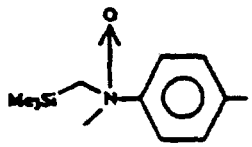
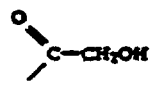
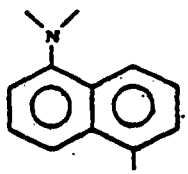
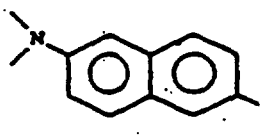
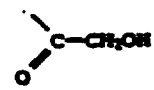
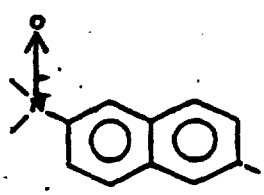
-continued

A	R_1	R_2	R_3	R_4
-	-	-	-	$-CH_2-CH=CH_2$
-	-	-	-	$-C\equiv C-H$
-		-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	$-OH$
-	-	-		$-H$
-		-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	$-OH$
-	-	-		$-H$
-		-	OH	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-		-	-	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-Cl$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	$-OH$
-	-	-		$-H$
-		-	-	-
-	-	-	$-C\equiv C-H$	$-OH$
-	-	-	$-OH$	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-Cl$
-	-	-	-	$-CH_2-C\equiv C-H$
-	Me_3SiCH_2-	-	-	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$

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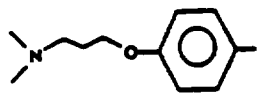
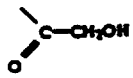
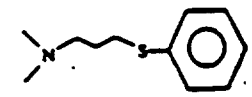
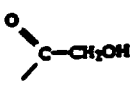
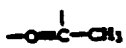
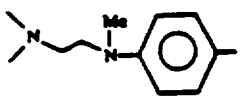
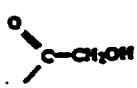
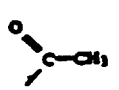
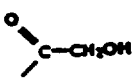
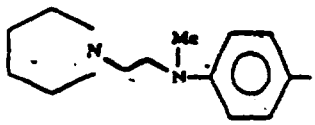
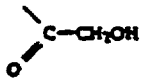
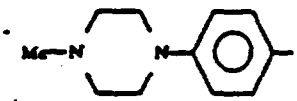
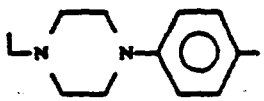
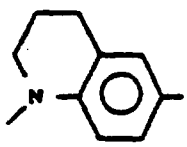
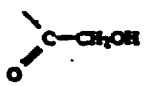
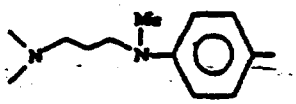
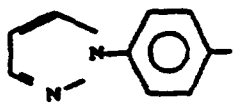
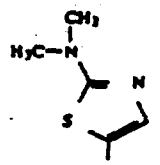
A	R_1	R_2	R_3	R_4
HO—N=(E)			—C≡C—H	—CH_2—C≡C—H
				—OH
HO—N=(Z)			OH	—C≡C—H
				—C≡C—CH_3
				—CH_2—C≡C—H
			—C≡C—H	—OH
			OH	—C≡C—H
				—C≡C—CH_3
				—CH_2—C≡C—H
O				—C≡C—CH_3
				—H
				
				
			OH	—C≡C—H
				—C≡C—CH_3
				—CH_2—C≡C—H
				—CH_2—CH=CH_2
				—CH_2CN
			—C≡C—H	—OH
				—H
				—CH_3
			OH	—H
			OH	—C≡C—H
				
				—C≡C—CF_3
				—C≡C—CH_2CH_3
				—C≡C—Cl
				—CH_2—C≡C—H
			—C≡C—H	—OH
				—H
				—CH_3
O		CH_2CH_3	OH	—C≡C—H
				—C≡C—CH_3
				—CH_2—C≡C—H
			—C≡C—H	—OH
				—H

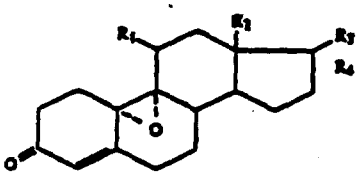
-continued

A	R_1	R_2	R_3	R_4
-		CH_3	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	-OH
-	-	-		-H
-		-	-	-
-	-	-	$-C\equiv C-H$	-OH
-	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	-	$-CH_2-CH=CH_2$
-	-	-	-	$-CH_2CN$
-		-	-	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	-	$-CH_2-CH=CH_2$
-	-	-	-	$-CH_2-CN$
-	-	-	$-C\equiv C-H$	-OH
-		-	-OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	-OH
-	-	-		-H
-		-	-	-
-	-	-	$-C\equiv C-H$	OH
-	-	-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	-	-H
-	-	-	-	$-CH_3$
-		-	-	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-CF_3$

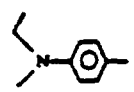
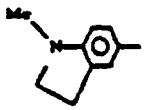
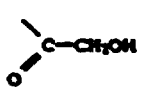
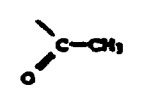
-continued

A	R_1	R_2	R_3	R_4
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	$-OH$
-		-	OH	$-C\equiv C-H$
-	-	-	-	$-C\equiv C-CH_3$
-	-	-	-	$-C\equiv C-CF_3$
-	-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-C\equiv C-H$	$-OH$
-	-	-	$-C\equiv C-CH_3$	$-OH$

(B) compounds of the formula



wherein R_1, R_2, R_3 and R_4 have the definitions in Table II

R_1	R_2	R_3	R_4
	CH_3	OH	$-C\equiv C-H$
-	-	-	$-C\equiv C-CH_3$
-	-	-	$-C\equiv C-CF_3$
-	-	-	$-CH_2CH_3$
-	-	-	$-CH_2-C\equiv C-H$
-	-	$-C\equiv C-H$	$-OH$
	-	OH	$-C\equiv C-H$
-	-	-	$-C\equiv C-CH_3$
-	-	-	$-C\equiv C-CF_3$
-	-	-	$-C\equiv C-CH_2CH_3$
-	-	-	$-CH_2-C\equiv C-H$
-	-	-	$-H$
-	-	-	$-CH_2CH_3$
-	-	$-C\equiv C-H$	$-OH$
-	-	-	$-H$
-		-	-
-	-	-	$-CH_3$
-		-	-

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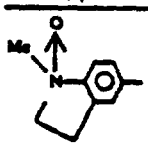
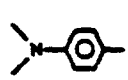
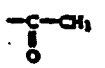
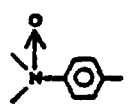
R_1	R_2	R_3	R_4
	-	-	-
-	-	OH	$-C\equiv C-H$
-	-	-	$-C\equiv C-CH_3$
-	-	-	$-C\equiv C-CF_3$
-	-	-	$-CH_2CH_3$
-	-	-	$-CH_2-C\equiv C-H$
-	-	$-C\equiv C-H$	$-OH$
-	-	OH	H
	-		CH_3
-	-	OH	$-C\equiv C-H$
-	-	-	$-C\equiv C-CH_3$
-	-	-	$-C\equiv C-CF_3$
-	-	-	$-CH_2CH_3$
-	-	-	$-CH_2-C\equiv C-H$
	-	-	$-C\equiv C-H$
-	-	-	$-C\equiv C-CH_3$
-	-	-	$-C\equiv C-CF_3$
-	-	-	$-CH_2-CH_3$
-	-	-	$-CH_2-C\equiv C-H$
-	-	-	H
-	-	-	CH_3
-	-	$-C\equiv C-H$	OH

Also prepared are the epoxides of the compounds of Table II.

The antiglucocorticoid compositions of the invention are comprised of an antiglucocorticoidally effective amount of at least one compound of formula I' and its non-toxic, pharmaceutically acceptable acid addition salts and an inert pharmaceutical carrier or excipient. The compositions may be in the form of tablets, dragees, gelules, granules, suppositories, injectable solutions or suspensions, pomades cremes and gel

Examples of suitable excipients are talc, gum arabic lactose, starch, magnesium stearate, cocoa butter, aque-

ous or non-aqueous vehicles, fatty bodies of animal or vegetable origin, paraffinic derivatives, glycols, diverse wetting agents, dispersants or emulsifiers and preservatives.

The compositions of the invention have remarkable antiglucocorticoid properties as can be seen from the pharmalogical data infra. The study of the products against hormonal receptors shows that the compositions possess progestomimetic activity or anti-progestomimetic, androgenic or antiandrogenic activity.

The compositions are used principally against secondary effects of glucocorticoids and are equally useful against troubles due to a hypersecretion of glucocorticoids and especially against aging in general and are particularly active against hypertension, atherosclerosis, osteoporosis, diabetes, obesity as well as depression of immunity and insomnia. The compositions of the invention also possess antiprogestomimetic activity and are useful for the preparation of original contraceptives and are equally useful against hormonal irregularities and they present an interest in the treatment of hormonodependent cancers.

Some of the compounds of formula I' and their acid addition salts also possess progestomimetic activity and are useful for the treatment of amenorrhea, dysmenorrhea and luteal insufficiencies.

The compositions of the invention also present antiandrogenic activity making them useful for the treatment of hypertrophia, prostate cancer, hyperandrogenia, anemia, hirsutism and acne.

The novel method of the invention of inducing antiglucocorticoid activity in warm-blooded animals, including humans, comprises administering to warm-blooded animals an antiglucocorticoidally effective amount of at least one compound of formula I' and their non-toxic, pharmaceutically acceptable acid addition salts. The usual daily dose is 0.15 to 15 mg/kg depending on the specific condition being treated and the compound used and the method of administration. The active compound may be administered orally, rectally, parenterally or locally.

In the following examples there are described several preferred embodiments to illustrate the invention. However, it is to be understood that the invention is not intended to be limited to the embodiments.

The antiprogestomimetic compositions of the invention contain a physiologically active quantity of at least one product of formula I and its pharmaceutically acceptable acid addition salts as antiprogestomimetics.

These compositions may be administered via the digestive tract, parenterally or locally, particularly in the vagina or via the endonasal route. They may be in the form of a simple tablet or lozenges, gelatin capsules, granulated suppositories, ovules, injectable preparations, ointments, creams or gels which are prepared according to the usual methods.

Excipients which may be employed are talc, gum arabic, lactose, starch, magnesium stearate, cocoa butter, animal and vegetable fats, paraffin derivatives, glycols, various wetting agents, dispersants, emulsifiers and preservatives.

The antiprogestomimetic compositions of the invention have remarkable properties as may be seen in the pharmacological tests which are described later.

The antiprogestomimetic compositions of the invention are used essentially to induce menses in female warm blooded animals.

The induction of menses during the luteal phase of the cycle and particularly at the end of the luteal phase permits the use of the compositions of the invention as contraceptives.

The antiprogrestomimetic compositions according to the invention may be equally used as agents to interrupt pregnancy since experiments with animals have demonstrated them to be abortive at any period of gestation.

The new method of the invention consists of inducing the menses in warm blooded female animals including women and is characterised in that one administers a quantity of antiprogestomimetic compound which is physiologically active such as a product of formula I'.

But it is understood that the essential role of progesterone is assigned during the luteal phase of the cycle at the moment of implantation of the embryo and during pregnancy.

The use of an antiprogestomimetic as an inducer of menstruation has been proposed, for example, in the tenth World Health Organization report page 80 and later in Chemtech, September 1977 page 566.

The method of utilization of this product is equally suggested as "post-coital and once-a-month drugs" in the report in WHO and in the expression "when taken monthly . . . will induce menstruation" in the Chemtech article.

Meanwhile before the products of formula I', no product having the required pharmacological properties for such a utilization had been synthesized.

The method of contraception according to the invention consists of administring to the woman about 10 mg to 1 gram of the product for 1 to 5 days preferably at the end of the menstrual cycle. Preferably one takes about 25 to 200 mg of the product per day.

Preferably the product is adminstered orally. Administration of the product via the vagina is equally suitable.

The method of using the products of the invention to interrupt pregnancy consists in administering to warm blooded females at least a physiologically active amount of the product of formula I'.

One administers an amount on the order of about 50 mg to 1 gram per day of the product for 1 to 5 days toward the end of the menstrual cycle. Preferably 200 mg to about 500 mg is used in women.

The preferred manner of administration of this product is orally or via the vagina.

The products of formula I' can be used in synchronizing the fertile periods of animals particularly cattle and sheep. They can also be used to control the fertility of pets dogs or cats.

Finally, the products of formula I', which have antiandrogen activity can be used for human contraception.

EXAMPLE 1

11β-(4-pyridyl)-17α-(prop-1-ynyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-17α-(prop-1-ynyl)-$\Delta^{5(10),9(11)}$-estradiene-17β-ol

207 ml of a solution of 1.15% ethyl magnesium bromide in tetrahydrofuran were stirred at 0° C. while bubbling gaseous propyne dried over calcium chloride therethrough for 90 minutes and the temperature was then allowed to return to room temperature. The mixture was stirred for one hour while the bubbling was continued. Then a solution of 30 g of 3,3-[1,2-ethanediyl-bisoxy]-$\Delta^{5(10),9(11)}$-estradiene-17-one in 120 ml of

anhydrous tetrahydrofuran and one drop of triethylamine was added to the mixture over 30 minutes and the mixture was stirred for 2 hours at room temperature and was then poured into a mixture of ice, distilled water and ammonium chloride. The stirred mixture was extracted 3 times with ether and the organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The residue was dried under reduced pressure to obtain 35.25 g of 3,3-[1,2-ethanediyl-bisoxy]-17α-(prop-1-ynyl)-$\Delta^{5(10),9(11)}$-estradiene-17β-ol.

NMR Spectrum (deuterochloroform):

Peaks at 0.83 ppm (hydrogens of 18-methyl); at 1.85 ppm (hydrogens of methyl of C≡C—CH_3); at 5.65 ppm (hydrogens of 11-carbon); at 4 ppm (hydrogens of ethylene ketal).

STEP B: 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol

A mixture of 30 g of the product of Step A in 150 ml of methylene chloride was stirred while bubbling nitrogen therethrough and after cooling the mixture to 0° C., 1.8 ml of hexafluoroacetone sesquihydrate were added all at once. The mixture was stirred while 4.35 ml of 85% oxygenated water were added and the mixture was stirred at 0° C. for 72 hours while continuing to bubble nitrogen therethrough. The solution was poured into a mixture of 250 g of ice and 500 ml of 0.2 N sodium thiosulfate solution and the mixture was stirred for a few moments and was then extracted with methylene chloride. The organic phase was washed with distilled water, dried over sodium sulfate in the presence of pyridine and evaporated to dryness under reduced pressure. The residue was dried under reduced pressure and the 31.6 g of residue were chromatographed over silica gel. Elution with a 9-1 benzene-ethyl acetate mixture yield 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(propyl-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol.

NMR Spectrum (deuterochloroform):

Peaks at 0.82 ppm (hydrogens of 18-CH_3); at 1.83 ppm (hydrogens of methyl of C≡C—CH_3); at 6.1 ppm (hydrogens of 11-carbon); at 3.92 ppm (hydrogens of ethylene ketal).

STEP C: 3,3-[1,2-ethanediyl-bisoxy]-11β-(4-pyridyl)-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

100 ml of a tetrahydrofuran solution of 0.5 to 0.6 M 4-chloropyridyl magnesium bromide prepared from 15 g of 4-chloro-pyridine and 6 g of magnesium was added at 20° C. to a solution of 6.16 g of dimethyl sulfide-cuprous bromide complex in 40 ml of tetrahydrofuran and the mixture was stirred under an inert atmosphere at room temperature for 20 minutes. Then, a solution containing 3.7 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol was added thereto over 10 minutes and the mixture was stirred at room temperature for one hour and was then poured into a mixture of cold water and ammonium chloride. The mixture was stirred at room temperature for 30 minutes and was extracted with ether. The organic phase was washed with an aqueous saturated sodium chloride solution, was dried and evaporated to dryness under reduced pressure. The 6 g of residue were chromatographed over silica gel and eluted with a 1-1 methylene chloride-acetone mixture containing 1 ppm of triethylamine to obtain 3.15 g of 3,3-[1,2-ethanediyl-bisoxyl]-11β-(4-pyridyl)-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol which was dried towards 60° C. at 0.1 mm Hg which had a specific rotation of $[\alpha]_D^{20} = -52° \pm 1.5°$ (c=1% in chloroform).

STEP D: 11β-(4-pyridyl)-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A solution of 2.9 g of the product of Step C, 14 ml of methanol and 7 ml of 2 N hydrochloric acid was stirred under an inert atmosphere at room temperature for 3 hours and was then admixed with a solution of 200 ml of ether and 90 ml of aqueous saturated sodium bicarbonate solution. The mixture was stirred at room temperature for 15 minutes and the decanted aqueous phase was extracted with ether. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness under reduced pressure. The 2.3 g of residue were chromatographed over silica gel and eluted with a 6-4 methylene chloride-acetone mixture. The 1.7 g of product was dried for 24 hours at 0.1 mm Hg and for 8 hours at 80° C. to obtain 11β-(4-pyridyl)-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +30.5° \pm 1°$ (c=1% in chloroform).

Using the same procedure, 11β-(3-pyridyl)-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +14°$ (c=1% in chloroform) and 11β-(2-pyridyl)-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = -2°$ (c=1% in chloroform) were prepared.

EXAMPLE 2

11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

12.33 g of dimethyl sulfide-cuprous bromide complex were added over 5 minutes at 0° C. to a solution of 0.85 M of 3-(N,N-dimethylamino)-propyl magnesium chloride [prepared from 42 g of chloro 3-(N,N-dimethylamino)-propane and 10.5 g of magnesium] and the mixture was stirred at 0° C. for 25 minutes. A solution of 3.70 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol in 50 ml of tetrahydrofuran was added to the mixture dropwise and the mixture was then stirred at 0° C. for 3 hours and was poured into a mixture of 40 g of ammonium chloride and 200 ml of iced water. The mixture was stirred at room temperature for 15 minutes and was then extracted with ether. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness under reduced pressure. The 4.6 g of residue were chromatographed over silica gel and eluted with an 8-2 methylene chloride-methanol mixture to obtain 2.55 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[3-(N,N-dimethylamino)-propyl]-17α-(Prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol with a specific rotation of $[\alpha]_D^{20} = -86° \pm 1.5°$ (c=1% in chloroform).

STEP B: 11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A mixture of 2.4 g of the product of Step A, 14 ml of methanol and 7 ml of 2 N hydrochloric acid was stirred under an inert atmosphere at room temperature for 4 hours and then 200 ml of isopropyl ether and 90 ml of aqueous saturated sodium bicarbonate solution were added thereto. The mixture was stirred at room temperature for 30 minutes and the decanted aqueous phase was extracted with ether. The organic extract was washed with aqueous saturated sodium chloride solution, was dried and evaporated to dryness under reduced pressure. The 1.8 g of residue were chromato-

graphed over silica gel and eluted with an 8-2 chloroform-methanol mixture. The 1.30 g of product were dried at 30° to 40° C. at 0.1 mm Hg to obtain 1.25 g of 11β-[3-(N,N-dimethylamino)-propyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = -114° \pm 2.5°$ (c = 1% in chloroform).

EXAMPLE 3

11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

A solution of 24 g of 4-(N,N-dimethylaminoethoxy)-bromobenzene was added dropwise over 45 minutes to 90 ml of anhydrous tetrahydrofuran and 2 ml of 1,2-dibromoethane were added as catalyst. After the addition, the mixture was stirred at 25° C. for one hour to obtain a solution of 0.7 M of 4-(N,N-dimethylaminoethoxy)-bromobenzene magnesium which was then added to a solution of 6.16 g of dimethylsulfide-cuprous bromide complex in 20 ml of tetrahydrofuran. The mixture was stirred at room temperature for 20 minutes and a solution of 3.7 g of 3,3-[1,2-(ethanediyl-bisoxy)]-5α,10α-epoxy-17α-prop-1-ynyl-$\Delta^{9(11)}$-estrene-17β-ol in 50 ml of tetrahydrofuran was added thereto dropwise over a few minutes. The mixture was stirred under an inert atmosphere for one hour and was then poured into a solution of 15 g of ammonium chloride in 20 ml of iced water. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, was dried and evaporated to dryness under reduced pressure. The 18.3 g of oil were chromatographed over silica gel and eluted with chloroform to obtain 4.5 g of 3,3-[1,2-(ethanediyl-bisoxyl)]-11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-66 ^{9}-estrene-5α,17β-diol with a specific rotation of $[\alpha]_D^{20} = -44° \pm 1.5°$ (c = 1% in chloroform).

STEP B: 11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

9.5 ml of 2 N hydrochloric acid were added to a solution of 4.5 g of the product of Step A in 20 ml of methanol and the solution was stirred at room temperature for 2 hours. 260 ml of ether and 110 ml of an aqueous saturated sodium bicarbonate solution were added to the mixture which was stirred at room temperature for 15 minutes. The decanted aqueous phase was extracted with ether and the organic phase was dried and evaporated to dryness under reduced pressure. The 3.3 g of residue were chromatographed over silica gel and eluted with a 92.5-7.5 methylene chloride-methanol mixture to obtain 1.8 g of amorphous 11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +71°$ (c = 1% in chloroform).

EXAMPLE 4

11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

A solution of 38 mmoles of p-dimethylaminophenyl magnesium bromide in tetrahydrofuran was added to a suspension of 4.1 g of a cuprous bromide-dimethylsulfide complex in 20 ml of tetrahydrofuran and then a solution of 2.45 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol in tetrahydrofuran was added thereto. The mixture was stirred for 10 minutes and was then hydrolyzed with 50 ml of aqueous saturated ammonium chloride solution. The decanted aqueous phase was extracted with ether and the organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The 11 g of residue were chromatographed over silica gel and eluted with a 6-4 cyclohexane-ethyl acetate mixture to obtain 1.8 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol which after crystallization from isopropyl ether and ethyl acetate had a specific rotation of $[\alpha]_D^{20} = -66.5°$ (c = 1% in chloroform) and a melting point of 210° C. and 750 mg of the corresponding 11α-compound.

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

2 ml of concentrated hydrochloric acid were added to a solution of 1.53 g of the product of Step A in 60 ml of methanol and after stirring the mixture for 30 minutes at room temperature, 150 ml of ether and then 50 ml of aqueous N sodium hydroxide solution were added thereto. The reaction mixture was stirred for 15 minutes and the decanted organic phase was dried and evaporated to dryness under reduced pressure. The 1.4 g of residue were chromatographed over silica gel and was eluted with a 7-3 cyclohexane-ethyl acetate mixture to obtain 0.932 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one melting at 150° C. and a specific rotation of $[\alpha]_D^{20} = +138.5°$ (c = 0.5% in chloroform).

EXAMPLE 5

11β-[4-trimethylsilyl-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-(4-trimethylsilyl-phenyl)-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

200 mg of caprous chloride were added under an inert atmosphere at −30° C. to 45 ml of solution of 0.65 M of 4-trimethylsilyl-phenyl magnesium bromide in tetrahydrofuran and a solution of 3.3 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol in 25 ml of tetrahydrofuran were added thereto dropwise at −20° C. After one hour, the mixture was hydrolyzed with aqueous ammonium chloride solution and was extracted with ether. The organic phase was dried and evaporated to dryness under reduced pressure and the residue was chromatographed over silica gel. Elution with a 94-6 methylene chloride-acetone mixture containing 0.1% of triethylamine yielded 2.087 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-(4-trimethylsilyl-phenyl)-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol which after crystallization from isopropyl ether and then ethyl acetate melted at 226° C. and a specific rotation of $[\alpha]_D^{20} = -60° \pm 1.5°$ (c = 0.9% in chloroform).

STEP B: 11β-(4-trimethylsilyl-phenyl)-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

1.7 g of Redex sulfonic acid resin were added to a solution of 1.68 g of the product of Step A in 17 ml of 90% alcohol and the mixture was refluxed for 30 minutes and vacuum filtered. The filter was rinsed with methylene chloride and the filtrate was evaporated to dryness under reduced pressure. The residue was taken up in methylene chloride and the solution was dried and

evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel and was eluted with an 85-15 benzene-ethyl acetate mixture to obtain 1.217 g of 11β-(4-trimethylsilyl-phenyl)-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one melting at 212° C. and having a specific rotation of $[\alpha]_D^{20} = +94°$ (c=0.9% in chloroform).

The same procedure was used to prepare 11β-[3-trimethylsilyl-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +52.5° \pm 2°$ (c=1% in chloroform).

EXAMPLE 6

11β-[4-(N,N-dimethylamino)-phenyl]-17β-ethynyl-$\Delta^{4,9}$-estradiene-17α-ol-3-one

STEP A: 3,3-dimethoxy-17β-ethynyl-$\Delta^{5(10),9(11)}$-estradiene-17α-ol

A mixture of 16.8 g of 3,3-dimethoxy-17α-ethynyl-$\Delta^{5(10),9(11)}$-estradiene-17β-ol, 175 ml of anhydrous tetrahydrofuran and 4.35 g of lithium bromide was stirred at room temperature for 5 minutes and then the mixture was cooled to −60° C. and 3.9 ml of methane sulfonyl chloride were added thereto. The mixture was stirred at −60° C. for one hour and was then poured into 500 ml of aqueous saturated ammonium chloride solution. The mixture was stirred for 10 minutes and was extracted with methylene chloride. The organic phase was dried and after the addition of 2.5 ml of pyridine, the mixture was evaporated to dryness at 0° C. under reduced pressure. 75 ml of tetrahydrofuran were added to the residue and 12.5 ml of 0.75 g of silver nitrate in water were added thereto. The mixture was held at −30° C. for 18 hours and at room temperature for 4 hours and was then poured into 500 ml of aqueous semisaturated ammonium chloride solution containing 5 g of sodium cyanide. The mixture was stirred at 20° C. for 30 minutes and was extracted with chloroform. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel and was eluted with a 9-1 petroleum ether-ethyl acetate mixture to obtain 3 g of 3,3-dimethoxy-17β-ethynyl-$\Delta^{5(10),9(11)}$-estradiene-17α-ol melting at ~150° C. and having a specific rotation of $[\alpha]_D^{20} = +125° \pm 2.5°$ (c=1% in chloroform).

STEP B: 3,3-dimethoxy-5α,10α-epoxy-17β-ethynyl-$\Delta^{9(11)}$-estrene-17α-ol

0.12 ml of hexachloroacetone and 0.65 ml of oxygenated water (200 volumes) were added at 0° C. to a mixture of 2.6 g of the product of Step A, 12 ml of methylene chloride and one drop of pyridine and the mixture was stirred for one hour after which 13 ml of chloroform were added. The mixture was stirred for 18 hours and was then poured into 100 ml of aqueous saturated sodium thiosulfate solution. The mixture was stirred for 10 minutes and was extracted with chloroform. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness under reduced pressure to obtain 2.8 g of 3,3-dimethoxy-5α,10α-epoxy-17β-ethynyl-$\Delta^{9(11)}$-estrene-17α-ol which was used as is for the next step. The product contained a small amount of the 5β,10β-epoxy compound.

STEP C: 3,3-dimethoxy-11β-[4-(N,N-dimethylamino)-phenyl]-17β-ethynyl-Δ^{9}-estrene-5α,17α-diol

A mixture of 2.8 g of the product of Step B, 56 ml of anhydrous tetrahydrofuran and 80 mg of anhydrous copper chloride was stirred under an inert atmosphere at room temperature for 5 minutes and was then placed in an ice bath. 33 ml of 0.95 M 4-dimethylaminophenyl magnesium bromide in tetrahydrofuran were added dropwise to the mixture which was then allowed to return to room temperature.

63 ml of 4-dimethylaminophenyl magnesium bromide were added to a suspension of 6.15 g of dimethylsulfide-copper bromide complex in 30 ml of anhydrous tetrahydrofuran while keeping the temperature below 28.5° C. and the mixture was stirred for 30 minutes. Then, the above solution was added dropwise thereto and the mixture was stirred at room temperature for 18 hours and was then poured into aqueous saturated ammonium chloride solution. The mixture was stirred for 10 minutes and was extracted with chloroform. The organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The residue was chromatographed over silica gel and was eluted with a 1-1 petroleum ether-ethyl acetate mixture containing 0.5 ppm of triethylamine. The 1.28 g of product was chromatographed over silica gel and was eluted with the same mixture to obtain 0.84 g of 3,3-dimethoxy-11β-[4-(N,N-dimethylamino)-phenyl]-17β-ethynyl-Δ^{9}-estrene-5α,17α-diol.

STEP D: 11β-[4-(N,N-dimethylamino)-phenyl]-17β-ethynyl-$\Delta^{4,9}$-estradiene-17α-ol-3-one

A mixture of 0.76 g of the product of Step C, 15 ml of methanol and 1.6 ml of 2 N hydrochloric acid was stirred for 90 minutes and was then poured into an aqueous saturated sodium bicarbonate. The mixture was extracted with chloroform and the organic phase was dried and evaporated to dryness under reduced pressure. The 0.76 g of residue was chromatographed over silica gel and was eluted with a 1-1 petroleum ether-ethyl acetate mixture and then with a 3-1 ether-petroleum ether mixture to obtain 0.435 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17β-ethynyl-$\Delta^{4,9}$-estradiene-17α-ol-3-one which after crystallization from isopropyl ether melted at 142° C. and had a specific rotation of $[\alpha]_D^{20} = +235.5° \pm 4.5°$ (c=0.45% in chloroform).

EXAMPLE 7

11β-[4-(N,N-dimethylamino)-phenyl]-17α-phenyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-$\Delta^{9(11)}$-estrene-17-one

2 drops of pyridine were added to a mixture of 11.18 g of 3,3-[1,2-ethanediyl-bisoxy]-$\Delta^{5(10),9(11)}$-estradiene-17-one and 56 ml of methylene chloride and 4.3 ml of hexafluoroacetone sesquihydrate were added to the mixture at 0° C. 1.6 ml of 85% oxygenated water were added to the mixture and the mixture was stirred under an inert atmosphere at 0° C. for 23 hours and was poured into a mixture of 200 g of ice and 200 ml of 0.5 M sodium thiosulfate solution. The mixture was stirred for 30 minutes and was extracted with methylene chloride containing a trace of pyridine. The organic phase was washed with water, dried and evaporated to dryness to obtain 11.4 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-$\Delta^{9(11)}$-estrene-17-one which was used as is for the next step.

STEP B: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-N,N-dimethylamino)-phenyl]-Δ^{9}-estrene-5α-ol-17-one

A mixture of 200 g of 4-dimethylamino benzene bromide in 950 ml of anhydrous tetrahydrofuran was added

over 24 hours at 35° C.±5° C. to a mixture of 29 g of magnesium turnings and 50 ml of anhydrous tetrahydrofuran under an inert atmosphere to obtain a solution of 0.8 M of magnesium.

284 ml of the said magnesium solution were added dropwise over 75 minutes at 0° to 5° C. under an inert atmosphere to a mixture of 25 g of the product of Step A, 500 ml of anhydrous tetrahydrofuran and 0.757 g of copper chloride and the mixture was stirred for 15 minutes and poured into aqueous saturated ammonium chloride solution. The mixture was extracted with ethyl acetate and the organic phase was washed with aqueous saturated ammonium chloride solution and with aqueous saturated sodium chloride solution, dried and evaporated to dryness under reduced pressure. The 46 g of residue were chromatographed over silica gel and were eluted with a 1-1 petroleum ether-ethyl acetate mixture containing 1 ppm of triethylamine to obtain 17.76 g of product melting at 178° C. The impure fractions were subjected again to chromatography over silica gel and were eluted with an 8-2 petroleum ether-acetone mixture containing 1 ppm of triethylamine to obtain another 6.35 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-Δ^9-estrene-5α-ol-17-one melting at 176° C. which was used as is for the next step.

STEP C: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-phenyl-Δ^9-estrene-5α,17β-diol

A solution of 4.51 g of the product of Step B in 45.1 ml of anhydrous tetrahydrofuran was added over 30 minutes at 25° C. to a solution of 33.3 ml of phenyllithium (1.5 moles) and the mixture was stirred for 4 hours at room temperature and was then poured into aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The 5.6 g of residue were chromatographed over silica gel and were eluted with a 9-1 methylene chloride-acetone mixture containing of triethylamine to obtain 1.16 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-phenyl-Δ^9-estrene-5α,17β-diol which after crystallization from an isopropyl ether-methylene chloride mixture melted at 240° C. and had a specific rotation of $[\alpha]_D^{20} = +53° \pm 2.5°$ (c=0.5% in $CHCl_3$).

STEP D: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-phenyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

3 ml of 2 N hydrochloric acid were added under an inert atmosphere at 0° to 5° C. to a mixture of 1.5 g of the product of Step C in 45 ml of methanol and the mixture was stirred at 0° to 5° C. for one hour. Then, 90 ml of ether and 90 ml of an aqueous 0.25 M of sodium bicarbonate solution were added to the mixture and the mixture was stirred for 5 minutes. The decanted aqueous phase was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The 1.3 g of residue were chromatographed over silica gel and were eluted with a 1-1 petroleum ether ether mixture to obtain 0.93 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-phenyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one which after crystallization from methylene chloride-isopropyl ether melted at 226° C. and had a specific rotation of $[\alpha]_D^{20} = +151.5°$ (c=0.4% in chloroform).

EXAMPLE 8

11β-[4-(N,N-dimethylamino)-phenyl]-23-methyl-19,21-dinor-17α-$\Delta^{4,9,23}$ cholatriene-20-yn-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-23-methyl-19,21-dinor-17α-$\Delta^{9,23}$-choladiene-20-yn-5α,17β-diol

10.61 ml of 2-methyl-1-buten-3-yne were added under an inert atmosphere to a mixture of 4.5 g of potassium tert.-butylate in 90 ml of anhydrous tetrahydrofuran and the mixture was stirred for 15 minutes at −10° C. A solution of 4.5 g of the product of Step B of Example 7 in 45 ml of anhydrous tetrahydrofuran was added over 15 minutes to the reaction mixture and the mixture was stirred at −10° C. for 30 minutes and then for 4 hours at 0° to 5° C. The mixture was poured into 500 ml of aqueous saturated solution of ammonium chloride and the mixture was extracted with ethyl acetate. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness to obtain 5.56 g of raw 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-23-methyl-19,21-dinor-17α-$\Delta^{9,23}$-choladiene-20-yn-5α,17β-diol melting at 205° C. which was used as is for the next step. The raw product was chromatographed over silica gel and was eluted with a 9-1 methylene chloride-ethyl acetate containing 1 part per 1000 of triethylamine and crystallized from ethyl acetate to obtain the product melting at 215° C.

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-23-methyl-19,21-dinor-17α-$\Delta^{4,9,23}$-cholatriene-20-yne-17β-ol-3-one

A mixture of 5 g of the product of Step A, 300 ml of methanol and 10 ml of 2 N hydrochloric acid was stirred under an inert atmosphere for 15 minutes at 20° C. and then 300 ml of methylene chloride and then 300 ml of aqueous 0.25 M sodium bicarbonate solution were added thereto. The mixture was stirred for 10 minutes and the decanted aqueous phase was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness. The 4.5 g of residue were chromatographed over silica gel and were eluted with a 1-1petroleum ether-ethyl acetate mixture to obtain after crystallization from diisopropyl oxide 2.01 g of 11β-[4-(N,N-dimethylamino)-phenyl]-23-methyl-19,21-dinor-17α-$\Delta^{4,9,23}$-cholatriene-20-yne-17β-ol-3-one melting at 185° C. and having a specific rotation of $[\alpha]_D^{20} = +88.5° \pm 1.5°$ (c=1% in $CHCl_3$).

EXAMPLE 9

11β-[4-(N,N-dimethylamino)-phenyl]-17β-methoxy-23-methyl-19,
21-dinor-17α-$\Delta^{4,9,23}$-cholatriene-20-yne-3-one

10.61 ml of 2-methyl-1-buten-3-yne were added dropwise at −10° C. to a suspension of 4.5 g of potassium tert.-butylate in 90 ml of anhydrous tetrahydrofuran under an inert atmosphere and the mixture was stirred at −10° C. for 15 minutes. Then, a mixture of 4.5 g of the product of Step B of Example 7 in 45 ml of anhydrous tetrahydrofuran was added over 15 minutes to the mixture which was then stirred at −10° C. for 30 minutes and at 0° to 5° C. for 4 hours. 7.5 ml of methyl iodide were added to the mixture which was then stirred in an ice bath for 30 minutes and then poured into 500 ml of 0.1 N hydrochloric acid. The mixture was stirred for 30 minutes at room temperature and was then extracted with ethyl acetate. The organic phase was washed with aqueous saturated sodium bicarbonate

solution, then with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 95-5 methylene chloride-ethyl acetate mixture to obtain 2.7 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17β-methoxy-23-methyl-19,21-dinor-17α-Δ^{4,9,23}-cholatriene-20-yne-3-one which after crystallization from methanol melted at 105° C.

EXAMPLE 10

11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^{4,9}-pregnadiene-20-yne-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^{9}-pregnene-20-yne-5α,17β-diol

A solution of 7 ml of trichloroethylene in 28 ml of anhydrous ether was added with stirring under an inert atmosphere at 0° to 5° C. to a mixture of 77.5 ml of 1 M butyllithium in hexane and 310 ml of anhydrous ether and the mixture was stirred for one hour while the temperature rose to 20° C. A solution of 7 g of Step B of Example 7 in 70 ml of tetrahydrofuran was added to the resulting mixture dropwise over 30 minutes at 0° to 5° C. and the mixture was stirred at 0° to 5° C. for 30 minutes after which the temperature was allowed to rise to 20° C. and was slowly poured into an aqueous saturated ammonium chloride solution and the decanted aqueous phase was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness to obtain 8.5 g of raw product melting at 220° C. The latter was added to 42.5 ml of diisopropyl oxide and the mixture was stirred for 30 minutes and vacuum filtered to obtain 6.38 g of product melting at 230° C. The latter was chromatographed over silica gel and was eluted with a 7-3 benzene-ethyl acetate mixture containing 1 ppm of triethylamine. The product was dissolved in methylene chloride and was precipitated by addition of diisopropyl oxide to obtain 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^{9}-pregnene-20-yne-5α,17β-diol melting at 240° C. and having a specific rotation of $[\alpha]_D^{20} = -83.5° \pm 1.5°$ (c=1% in $CHCl_3$).

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^{4,9}-pregnadiene-20-yne-17β-ol-3-one

15 ml of 2 N hydrochloric acid were added under an inert atmosphere to a mixture of 6.38 g of the product of Step A in 191.4 ml of 95% ethanol and after stirring the mixture for one hour, 300 ml of methylene chloride and then 200 ml of aqueous 0.25 mM sodium bicarbonate solution were added thereto. The decanted aqueous phase was extracted with methylene chloride and the organic phase was washed with water, dried and evaporated to dryness under reduced pressure. The 6 g of residue was chromatographed over silica gel and were eluted with a 7-3 benzene-ethyl acetate mixture to obtain 3.95 g of 11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^{4,9}-pregnadiene-20-yne-17β-ol-3-one which after crystallization from ethyl acetate melted at 240° C. and had a specific rotation of $[\alpha]_D^{20} = +111° \pm 2°$ (c=1% in chloroform).

EXAMPLE 11

N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^{4,9}-pregnadiene-20-yne-17β-ol-3-one

A mixture of 0.54 g of 85% M-chloroperbenzoic acid in 10.8 ml of methylene chloride was added under an inert atmosphere at 0° to 5° C. to a mixture of 1.2 g of the product of Example 10 in 24 ml of methylene chloride and the mixture was stirred for one hour at 0° to 5° C. and was then poured into aqueous 0.2 N sodium thiosulfate solution. The mixture was extracted with methylene chloride and the organic phase was washed with aqueous saturated sodium bicarbonate solution, with water, dried and evaporated to dryness. The 1.3 g of residue was chromatographed over silica gel and was eluted with a 7-3 methylene chloride-methanol mixture to obtain 1.15 g of N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^{4,9}-pregnadiene-20-yne-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +47.5° \pm 1.5°$ (c=0.7% in chloroform).

EXAMPLE 12

N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-9α,10α-epoxy-21-chloro-19-nor-17α-Δ^{4}-pregnene-20-yne-17β-ol-3-one

A mixture of 1.17 g of 85% m-chloroperbenzoic acid in 23.4 ml of methylene chloride was added over 15 minutes at 0° to 5° C. to a solution of 1.18 g of the product of Example 10 in 23.6 ml of methylene chloride and the mixture was stirred for 2 hours at 20° C. after which another 1.17 g of 85% M-chloroperbenzoic acid were added. The mixture was stirred for one hour and was poured into a solution of aqueous 0.2 N sodium thiosulfate. The mixture was extracted with methylene chloride and the organic phase was washed with aqueous saturated sodium bicarbonate solution and then with water, dried and evaporated to dryness to obtain 1.14 g of residue melting at 220° C. The residue was chromatographed over silica gel and was eluted with an 8-2 methylene chloride-methanol mixture to obtain 1 g of N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-9α,10α-epoxy-21-chloro-19-nor-17α-Δ^{4}-pregene-20-yne-17β-ol-3-one melting at 270° C. and having a specific rotation of $[\alpha]_D^{20} = +39.5° \pm 2.5°$ (c=0.5% in chloroform).

EXAMPLE 13

9α,10α-epoxy-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^{4}-pregnene-20-yne-17β-ol-3-one

0.34 g of triphenylphosphine were added under an inert atmosphere to a mixture of 0.63 g of the product of Example 12 in 6.3 ml of acetic acid and the mixture was stirred at room temperature for 45 minutes and was then poured into water. The mixture was extracted with methylene chloride and the organic phase was washed with water, dried and evaporated to dryness. The 0.9 g of residue was chromatographed over silica gel and was eluted with a 1-1 petroleum ether-ethyl acetate mixture. The product was crystallized from a methylene chloride-isopropyl ether mixture to obtain 0.346 g of 9α,10α-epoxy-11β-[4-(N,N-dimethylamino)-phenyl]-21-chloro-19-nor-17α-Δ^{4}-pregnene-20-yne-17β-ol-3-one melting at 265° C. and having a specific rotation of $[\alpha]_D^{20} = +45° \pm 2°$ (c=0.8% in chloroform).

EXAMPLE 14

11β-[4-(N,N-dimethylamino)-phenyl]-21-phenyl-19-nor-17α-Δ4,9-pregnadiene-20-yne-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethyl-amino)-phenyl]-21-phenyl-19-nor-17α-Δ9-pregnene-20-yne-5α,17 diol

A mixture of 4.17 g of potassium tert.-butylate in 83 ml of anhydrous tetrahydrofuran was stirred under an inert atmosphere for 10 minutes and then 4.5 ml of phenyl acetylene were added dropwise at −10° C. The suspension was stirred for 5 minutes and then a solution of 4.17 g of the product of Step B of Example 7 in 41 ml of anhydrous tetrahydrofuran was added thereto dropwise at −10° C. Then, the temperature rose to 0° C. and held there for one hour and was then poured into an aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The 4.7 g of residue were chromatographed over silica gel and eluted with a 95-5 methylene chloride-acetone mixture to obtain 3.71 of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4,(N,N-dimethylamino-phenyl]-21-phenyl-19-nor-17α-Δ9-pregnene-20-yne-5α,17β-diol melting at 168° C. and having a specific rotation of $[\alpha]_D^{20} = -119.5° \pm 2°$ (c=1% in chloroform).

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-21-phenyl-19-nor-17α-Δ4,9-pregnadiene-20-yne-17β-ol-3-one

6.3 ml of 2 N hydrochloric acid were added to a solution of 3.49 g of the product of Step A in 68 ml of methanol and the mixture was stirred for 30 minutes and was poured into a mixture of 180 ml of ether and 90 ml of aqueous 0.25 M sodium bicarbonate solution. The mixture was stirred for 5 minutes and the decanted aqueous phase was extracted with ether. The organic phase was washed with aqueous 0.25 M sodium bicarbonate solution, then with aqueous sodium chloride, dried and evaporated to dryness. The 4.35 g of residue were chromatographed over silica gel and eluted with with a 95-5 methylene chloride-acetone mixture to obtain 2.13 g of 11β-[4-(N,N-dimethylamino)-phenyl]-21-phenyl-19-nor-17α-Δ4,9-pregnadiene-20-yne-17β-ol-3-one which after crystallization from isopropyl ether had a specific rotation of $[\alpha]_D^{20} = +22.5° \pm 1°$ (c=1% in chloroform).

EXAMPLE 15

11β-[4-(N,N-dimethylamino)-phenyl]-17α-(propa-1,2-dienyl)-Δ4,9-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(propa-1,2-dienyl)-Δ9-estrene-5α,17β-diol and 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)phenyl]-17α-(prop-2-ynyl)-Δ9-estrene-5α,17β-diol

Allene was bubbled into 50 ml of anhydrous tetrahydrofuran at 0° to 5° C. until 2.1 g were absorbed and 23.9 ml of a solution of a 1.3 M of butyllithium in hexane were added thereto over 15 minutes at −70° C. The mixture was stirred at −70° C. for 15 minutes and then a solution of 3.5 g of the product of Step B of Example 7 in 35 ml of anhydrous tetrahydrofuran were added thereto at −70° C. over 25 minutes. The mixture was stirred at −70° C. for one hour and was poured slowly into an iced aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The 3.4 g of residue were chromatographed over silica gel and eluted with a 1-1 petroleum ether-ethyl acetate mixture containing 1 ppm of triethylamine to obtain 1.73 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(propa-1,2-dienyl)-Δ9-estrene-5α,17β-diol melting at 178° C. and having a specific rotation of $[\alpha]_D^{20} = -32° \pm 2°$ (c=0.7% in chloroform) and 1.5 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-Δ9-estrene-5α,17β-diol melting at 150° C. and having a specific rotation of $[\alpha]_D^{20} = -15° \pm 2°$ (c=0.9% in chloroform).

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(propa-1,2-dienyl)-Δ4,9-estradiene-17β-ol-3-one

A mixture of 1.73 g of the 17α-(propa-1,2-dienyl)-isomer of Step A, 51.8 ml of 95% ethanol and 3.5 ml of 2 N hydrochloric acid was stirred under an inert atmosphere at 20° C. for one hour and then 50 ml of methylene chloride and 50 ml of aqueous 0.25 M sodium bicarbonate solution were added thereto. The decanted aqueous phase was extracted with methylene chloride and the organic phase was washed with water, dried and evaporated to dryness. The 1.51 g of residue were dissolved in 10 ml of hot methylene chloride and 15 ml of isopropyl ether were added to the solution. The mixture was concentrated and allowed to stand to obtain 1.23 g of product which were crystallized form a methylene chloride-isopropyl ether mixture to obtain 1.11 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(propa-1,2-dienyl)-Δ4,9-estradiene 17β-ol-3-one melting at 228° C. and having a specific rotation of $[\alpha]_D^{20} = +139.5° \pm 3°$ (c=0.8% in chloroform).

EXAMPLE 16

11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-Δ4,9-estradiene-17β-ol-3-one

A mixture of 0.94 g of the 17α-(prop-2-ynyl)-isomer of Step A of Example 15, 28.2 ml of 95% ethanol and 2 ml of 2 N hydrochloric acid was stirred at 20° C. for one hour and then 50 ml of methylene chloride and 50 ml of an aqueous 0.25 M sodium bicarbonate solution were added thereto. The mixture was stirred for 5 minutes and the decanted aqueous phase was extracted with methylene chloride. The organic phase was washed with water, dried and evaporated to dryness and the residue was chromatographed over silica gel. Elution with a 1-1 petroleum ether-ethyl acetate mixture yielded 0.42 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-ynyl)-Δ4,9-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +143° \pm 3°$ (c=0.8% in chloroform).

EXAMPLE 17

11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-Δ4,9-estradiene 17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17β-cyano-17α-trimethylsilyloxy-Δ9-estrene-5-α-ol

A solution of 18 mmoles of [4-(N,N-dimethylamino)-phenyl]-magnesium bromide in anhydrous tetrahydrofuran was added under an inert atmosphere to a suspension of 2.05 g of dimethylsulfide-copper bromide complex in 10 ml of anhydrous tetrahydrofuran and the mixture was stirred for 30 minutes after which 20 ml of anhydrous triethylamine were added thereto. A solu-

tion of 0.95 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17β-cyano-17α-trimethylsilyloxy-$\Delta^{9(11)}$-estrene in anhydrous tetrahydrofuran were added to the mixture which was then stirred for 15 hours at room temperature and poured into 50 ml of aqueous saturated ammonium chloride solution. The decanted aqueous phase was extracted with ether and the organic phase was washed with water, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with an 8-2 benzene-ethyl acetate mixture to obtain 1.1 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17β-cyano-17α-trimethylsilyloxy-Δ^9-estrene-5α-ol which after crystallization from isopropyl ether melted at 247° C. and had a specific rotation of $[\alpha]_D^{20} = -12.5°$ (c=1% in chloroform).

STEP B: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-Δ^9-estrene-5α,17β-diol

1 g of the acetylide complex of lithium ethylenediamine was added to a mixture of 0.8 g of the product of Step A in 8 ml of ethylenediamine and the mixture was stirred under an inert atmosphere at −50° C. for 90 minutes. The mixture was cooled to 20° C. and was poured into aqueous ammonium chloride solution. The mixture was extracted with ether and methylene chloride and the organic phase was dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 7-3 benzene-ethyl acetate mixture. The product was crystallized from isopropyl ether to obtain 0.43 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-Δ^9-estrene-5α,17β-diol melting at 199° C. and having a specific rotation of $[\alpha]_D^{20} = -43° \pm 1.5°$ (c=1% in chloroform).

STEP C: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

1 ml of 2N hydrochloric acid was added to a solution of 0.25 g of the product of Step B in 6 ml of methanol and the mixture was stirred at 20° C. for 40 minutes and then was poured into water containing 2.5 ml of N sodium hydroxide. The mixture was extracted with ether and the organic phase was dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 7-3 benzene-ethyl acetate mixture to obtain 0.25 of 11β-[4-(N,N-dimethylamino)phenyl]-17α-ethynyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one.

Analysis: $C_{28}H_{33}NO_2$; molecular weight=415.54: Calculated: %C 80.92; %H 8.00; %N 3.37. Found: %C 80.7; %H 8.1; %N 3.1.

EXAMPLE 18

11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-Δ^9-estrene-5α,17β-diol

12.25 g of the acetylide complex of lithium ethylenediamine were added under an inert atmosphere to a solution of 6 g of the product of Step B of Example 7 in 180 ml of tetrahydrofuran and the mixture was stirred at 55° C. for 4 hours and was then cooled and poured into 600 ml of an iced aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and eluted with a 7-3 benzene-ethyl acetate mixture containing 1 ppm of triethylamine. The 4.5 g of product was crystallized from a methylene chloride-diisopropyl oxide mixture to obtain 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-Δ^9-estrene-5α,17β-diol melting at 202° C. and having a specific rotation of $[\alpha]_D^{20} = -47.5° \pm 1.5°$ (c=1% in chloroform).

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

5 ml of 2 N hydrochloric acid were added to a suspension of 2 g of the product of Step A in 50 ml of 95% ethanol and the mixture was stirred at 20° C. for one hour. 100 ml of ether and then 100 ml of aqueous 0.25 M sodium bicarbonate solution were added to the mixture and the decanted aqueous phase was extracted with ether. The organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness and the residue was chromatographed over silica gel. Elution with a 6-4 petroleum ether-ethyl acetate mixture yielded 1.52 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethynyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one which after crystallization from diisopropyl oxide melted at 172° C. and had a specific rotation of $[\alpha]_D^{20} = +182° \pm 2.5°$ (c=1% in chloroform).

EXAMPLE 19

11β-[3-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[3-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol

A mixture of 10 g of m-bromo-dimethylaniline in 45 ml of anhydrous tetrahydrofuran was added under an inert atmosphere over 45 minutes to a mixture of 1.46 g of magnesium and 5 ml of anhydrous tetrahydrofuran and the reaction was started by addition of dibromomethane. The mixture was stirred for one hour to obtain a solution of 0.95 M of magnesium and 42.2 ml of the solution were added at 0° to 5° C. over 30 minutes under an inert atmosphere to a mixture of 3.7 g of 3,3-[1,2-ethanediyl-bisoxyl-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol, 74 ml of anhydrous tetrahydrofuran and 99 mg of copper chloride and the mixture was stirred for 30 minutes at 0° to 5° C. and was poured into an aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and eluted with a 9-1 methylene chloride-acetone mixture containing 1 part per 1000 triethylamine to obtain 3.5 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[3-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl]-Δ^9-estrene-5α,17β-diol melting at 262° C. and having a specific rotation of $[\alpha]_D^{20} = -64° \pm 1.5°$ (c=1% in chloroform) and 0.66 g of the corresponding 5β-ol isomer melting at 210° C. and having a specific rotation of $[\alpha]_D^{20} = +32.5° \pm 1°$ (c=0.8% in chloroform).

STEP B: 11β-[3-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

10 ml of 2 N hydrochloric acid were added at 0° to 5° C. under an inert gas to a mixture of 3.3 g of the product of step A in 100 ml of methanol and the mixture was stirred at 0° to 5° C. for one hour. 200 ml of diethyl oxide and then 200 ml of aqueous 0.25 M sodium bicarbonate solution were added to the mixture which was

then stirred for 5 minutes. The decanted aqueous phase was extracted with diethyloxide and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The 3 g of residue were chromatographed over silica gel and eluted with a 7-3 benzene-ethyl acetate mixture to obtain 1.43 g of amphorous 11β-[3-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +43° \pm 2.5°$ (c=1% in $CHCl_3$).

EXAMPLE 20

N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A solution of 0.71 g of 85% m-chloroperbenzoic acid in 14.2 ml of methylene chloride was added over 10 minutes at 0° to 5° C. to a mixture of 1.5 g of the product of Example 4 in 30 ml of methylene chloride and the mixture was stirred for one hour at 0° to 5° C. and was poured into 100 ml of an aqueous 0.2 N sodium thiosulfate solution. The decanted aqueous phase was extracted with methylene chloride and the organic phase was washed with aqueous 0.5 M sodium bicarbonate solution, dried and evaporated to dryness. The residue was dissolved in 20 ml of methylene chloride and 20 ml of diisopropyl oxide were added thereto. Crystallization was induced and the mixture stood for a while and was vacuum filtered. The crystals were dried to obtain 1.4 g of N-oxide of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one melting at 210° C. and having a specific rotation of $[\alpha]_D^{20} = +73.5° \pm 2°$ (c=1% in chloroform).

EXAMPLE 21

11β-[4-(N,N-dimethylamino)-phenyl]-$\Delta^{4,9}$-estradiene-17β-ol-3-one

106 mg of sodium borohydride were added to a solution of 1 g of the product of Step B of Example 7 in 20 ml of tetrahydrofuran containing 10% water and the mixture was stirred for one hour and poured into 200 ml of water. The mixture was extracted with methylene chloride and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness to obtain 1.3 g of 11β-[4-(N,N-dimethylamino)-phenyl]-$\Delta^{4,9}$-estradiene-5α,17β-diol-3-one. 0.63 g of the latter were added to a mixture of 12 ml of methanol and 2.4 ml of 2 N hydrochloric acid and the mixture was stirred at room temperature for 90 minutes and was poured into aqueous sodium bicarbonate. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 6-4 petroleum ether-ethyl acetate mixture. The residue was triturated with petroleum ether and vacuum filtered to obtain 0.38 g of 11β-[4-(N,N-dimethylamino)-phenyl]-$\Delta^{4,9}$-estradiene-17β-ol-3-one melting at 130° C. and having a specific rotation of $[\alpha]_D^{20} = +277° \pm 5°$ (c=0.5% in chloroform).

EXAMPLE 22

11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-enyl)-$\Delta^{4,9}$-estradien-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-enyl)-Δ^{9}-estrene-5α,17β-diol

A solution of 3.5 g of the product of Step B of Example 7 in 35 ml of tetrahydrofuran was added under an inert atmosphere at 20° C. over 15 minutes to 55.5 ml of 0.7 M allyl magnesium bromide in ether and the mixture was stirred at 20° C. for one hour and was then poured into an aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was dissolved in 10 ml of methylene chloride and 15 ml of diisopropyl oxide were added to the solution which was then concentrated and allowed to stand. The mixture was vacuum filtered and the crystals were rinsed with diisopropyl oxide and dried to obtain 2.76 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-enyl)-Δ^{9}-estrene-5α,17β-diol melting at 198° C.

Analysis: $C_{31}H_{43}NO_4$; molecular weight=493.69; Calculated: %C 74.42; %H 8.78; %N 2.83. Found: %C 74.0; %H 8.7; %N 2.9.

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-enyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

4.5 ml of 2 N hydrochloric acid were added to a suspension of 2.2 g of the product of Step A in 66 ml of methanol and the mixture was stirred at 20° C. for 30 minutes after which 132 ml of diethyl oxide and then 132 ml of aqueous 0.25 M sodium bicarbonate solution were added thereto. The decanted aqueous phase was extracted with diethyl oxide and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 7-3 benzene-ethyl acetate mixture. The product was taken up in a mixture of 15 ml of diisopropyl oxide and 7.5 ml of methylene chloride and the solution was concentrated and allowed to stand. The mixture was vacuum filtered and the crystals were rinsed with diisopropyl oxide and dried to obtain 1.365 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-2-enyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one melting at 182° C. and having a specific roation of $[\alpha]_D^{20} = +206.5° \pm 3°$ (c=1% in chloroform).

EXAMPLE 23

11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

A solution of 42.8 g of 4-(N,N-dimethylaminomethyl)bromobenzene in 190 ml of anhydrous tetrahydrofuran was added over 90 minutes under an inert atmosphere at 45° to 50° C. to a mixture of 5.5 g of magnesium in 10 ml of anhydrous tetrahydrofuran and the reaction was induced with dibromoethane addition. The mixture was stirred for one hour to obtain an 0.85 M magnesium solution and 127 ml of the said solution were added under an inert atmosphere at 0° to 5° C. over one hour to a mixture of 10 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-

estrene-17β-ol, 200 ml of anhydrous tetrahydrofuran and 0.27 g of copper chloride. The mixture was stirred for 15 minutes and was poured into an aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 9-1 methylene chloride-methanol mixture containing 1 part per 1000 of triethylamine to obtain 10.1 g of product. The latter was dissolved in methylene chloride and a few drops of methanol and then diisopropyl oxide were added thereto. The mixture was concentrated, allowed to stand for 6 hours and was vacuum filtered to obtain 7.37 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol melting at 186° C. and having a specific rotation of $[\alpha]_D^{20} = -63° \pm 2.5°$ (c=0.5% in chloroform).

STEP B: 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A mixture of 15 ml of 2 N hydrochloric acid, 7.37 g of the product of Step A and 147.4 ml of methanol was stirred at 20° C. for one hour and then 300 ml of diethyl oxide and 300 ml of aqueous 0.25 M sodium bicarbonate solution were added thereto. The decanted aqueous phase was extracted with diethyl oxide and the organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The product was dissolved in a mixture of diisopropyl oxide and methylene chloride and the solution was concentrated and allowed to stand. The mixture was vacuum filtered and the crystals were dried to obtain 3.74 g of 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one melting at 190° C. and having a specific rotation of $[\alpha]_D^{20} = +84.5° \pm 2°$ (c=0.8% in chloroform).

EXAMPLE 24

11β-(4-pyrrolidinyl-phenyl)-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-(4-pyrrolidinylphenyl)-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol

A solution of 34 g of 4-pyrrolidinyl-bromobenzene in 140 ml of anhydrous tetrahydrofuran was added over one hour under an inert atmosphere at 45°-50° C. to a mixture of 4 g of magnesium and 10 ml of anhydrous tetrahydrofuran and the reaction was started by addition of dibromoethane to obtain a 1 M magnesium solution. 86.4 ml of the said solution were added over 90 minutes at 0° to 5° C. under an inert atmosphere to a mixture of 8 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol in 160 ml of anhydrous tetrahydrofuran and 216 mg of copper chloride and the mixture was stirred for one hour and was poured into an aqueous saturated ammonium chloride solution. The mixture was extracted with diethyl oxide and the organic phase was washed with aqueous saturated ammonium chloride solution, aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 95-5 methylene chloride-acetone mixture containing part per 1000 of triethylamine to obtain 8.3 g of 3,3-[1,2-ethanediylbisoxy]-11β-(4-pyrrolidinyl-phenyl)-17α-(prop-1-ynyl)-Δ^{9}-estrene-5α,17β-diol which after crystallization from a methylene chloride-isopropyl ether mixture melted at 185° C. and had a specific rotation of $[\alpha]_D^{20} = -67° \pm 1.5°$ (c=1% in chloroform).

STEP B: 11β-(4-pyrrolidinyl-phenyl)-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A mixture of 13 ml of 2 N hydrochloric acid, 6.4 g of the product of Step A and 128 ml of methanol was stirred at 20° C. for one hour and then 256 ml of diethyl oxide and 256 ml of aqueous 0.25 M sodium bicarbonate solution were added thereto. The decanted aqueous phase was extracted with diethyl oxide and the organic phase was washed with aqueous 0.25 M sodium bicarbonate solution, with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 1—1 petroleum ether-ethyl acetate mixture to obtain 5.25 g of 11β-(4-pyrrolidinyl-phenyl)-17α-(prop-1-ynyl) $\Delta^{4,9}$-estradiene-17β-ol-3-one which after crystallization from a methylene chloride-diisopropyl oxide mixture melted at 190° C. and had a specific rotation of $[\alpha]_D^{20} = +120° \pm 2.5°$ (c=1.2% in chloroform).

EXAMPLE 25

11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethenyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethenyl-Δ^{9}-estrene-5α,17β-diol

A current of hydrogen was passed for one hour through a mixture of 3 g of the product of Step B of Example 17, 60 ml of anhydrous pyridine and 0.6 g of 5% palladized calcium carbonate at room temperature and the mixture was then vacuum filtered. The filtrate was evaporated to dryness and the residue was taken up in toluene. The solution was evaporated to dryness to obtain 2.94 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethenyl-Δ^{9}-estrene-5α,17β-diol melting at 181° C. which was used as is for the next step. A sample after crystallization from a mixture of methylene chloride-diisopropyl oxide melted at 182° C. and had a specific rotation of $[\alpha]_D^{20} = -6.5° \pm 2°$ (c=0.7% in chloroform).

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethenyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A mixture of 6.2 ml of 2 N hydrochloric acid, 2.94 g of the product of Step A and 60 ml of methanol was stirred at 20° C. for one hour and then 120 ml of ether and 120 ml of aqueous 0.25 M sodium bicarbonate solution were added thereto. The mixture was stirred for 10 minutes and the decanted aqueous phase was extracted with ether. The organic phase was washed with aqueous 0.25 M sodium bicarbonate solution, aqueous saturated sodium chloride solution, dried and evaporated to dryness. The 2.65 g of residue were chromatographed over silica gel and eluted with a 7-3 benzene-ethyl acetate mixture. The product was crystallized from a diisopropyl oxide-methylene chloride mixture to obtain 1.51 g of 11β-[4-(N,N-dimethylamino)-phenyl]-17α-ethenyl-$\Delta^{4,9}$-estradiene-17β-ol-3-one melting at 150° C. and having a specific rotation of $[\alpha]_D^{20} = +243° \pm 3°$ (c=0.8% in chloroform).

EXAMPLE 26

11β-[4-(N,N-diethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 4-(N,N-diethylamino)-bromobenzene

93 g of bromine were added dropwise to a solution of 66 g of N,N-diethylaniline in 400 ml of acetic acid and the mixture was poured into an ice-water mixture. The mixture was extracted with methylene chloride and the organic phase was washed with aqueous sodium bicarbonate solution, dried and evaporated to dryness to obtain 125 g of 4-(N,N-diethylamino)-bromobenzene boiling at 97° C. at 0.6 mm Hg.

STEP B: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-diethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol

A solution of 34.2 g of 4-(N,N-diethylamino)-bromobenzene in 110 ml of tetrahydrofuran was added at 35° C. under an inert atmosphere to a mixture of 3.9 g of magnesium and 10 ml of tetrahydrofuran to obtain a 1 M magnesium solution and 80 ml of the said solution was slowly added with stirring at 0° to 5° C. under an inert atmosphere to a solution of 7.4 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol, 150 ml of anhydrous tetrahydrofuran and 0.25 g of copper chloride. The mixture was stirred at 20° C. for 17 hours and was then poured into an aqueous ammonium chloride solution. The mixture was extracted with ether and the organic phase was washed with aqueous sodium bicarbonate solution, dried and evaporated to dryness. The residue was empasted with petroleum ether and treated with activated carbon in ether. The product was crystallized from isopropyl ether to obtain 4 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-diethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol with a specific rotation of $[\alpha]_D^{20} = -61° \pm 2.5°$ (c=0.7% in $CHCl_3$).

STEP C: 11β-[4-(N,N-diethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A mixture of 8 ml of 2 N hydrochloric acid, 3.12 g of the product of Step B and 45 ml of methanol was stirred at 20° C. under an inert atmosphere for 45 minutes and was then poured into water. The mixture was neutralized by addition of 2 N sodium hydroxide solution and was extracted with methylene chloride. The organic phase was dried and evaporated to dryness and the residue was chromatographed over silica gel. Elution with a 1-1 benzene-ethyl acetate mixture yielded 1.34 g of 11β-[4-(N,N-diethylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +144.5° \pm 3°$ (c=0.8% in chloroform).

Analysis: $C_{31}H_{39}NO_2$; molecular weight=457.63. Calculated: %C 81.36; %H 8.59; %N 3.06. Found: %C 81.7; %H 8.8; %N 2.09.

EXAMPLE 27

11β-[4-(N-methyl-N-3-methylbutylamino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: N-methyl-N-(3-methylbutyl)-aniline

121 g of isoamyl bromide were added dropwise to a mixture of 86 g of N-methyl-aniline, 500 ml of anhydrous benzene and 81 g of anhydrous triethylamine and the mixture was refluxed for 100 hours and was filtered. The filtrate was washed with water, dried and evaporated to dryness. The residue was distilled to obtain 90 g of N-methyl-N-(3-methylbutyl)-aniline boiling at 132° C. at 18 mm Hg.

STEP B: N-methyl-N-(3-methylbutyl)-4-bromo-aniline

A solution of 58 g of bromine in 60 ml of acetic acid was added dropwise at about 15° C. over one hour to a mixture of 64 g of the product of Step A in 300 ml of acetic acid and the mixture was stirred at 80° C. for 8 hours and was poured into iced water. The mixture was extracted with methylene chloride and the organic phase was washed with aqueous sodium bicarbonate, with water, dried and evaporated to dryness. The residue was distilled to obtain 70 g of N-methyl-N-(3-methylbutyl)-4-bromo-aniline boiling at 119° C. at 0.5 mm Hg.

STEP C: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N-methyl-N-3-methylbutylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol

A few ml of a solution of the product of Step B in tetrahydrofuran were added under an inert atmosphere to a mixture of 4.12 g of magnesium and 10 ml of tetrahydrofuran and the reaction was started by addition of 0.2 ml of 1,2-dibromoethane. The rest of the solution of the product of Step B in anhydrous tetrahydrofuran (32.6 g in 90 ml) was added over 40 minutes to the mixture and after the temperature returned to room temperature, the mixture was stirred for one hour to obtain an 0.9 M magnesium solution. A mixture of 3.77 g of copper chloride, 8 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol and 90 ml anhydrous tetrahydrofuran was stirred under an inert atmosphere at 5° C. for 20 minutes and then 100 ml of the magnesium solution were added thereto. The mixture was poured into aqueous ammonium chloride solution and was extracted with ether containing triethylamine and then with methylene chloride containing triethylamine. The combined organic phases were washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness to obtain 31.2 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N-methyl-N-3-methylbutylamino)-phenyl]-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol which was used as is for the next step. A sample of the product was chromatographed over silica gel and was eluted with a 96.5-4.5-0.5 methylene chloride-acetone-triethylamine mixture to obtain the compound with a specific rotation of $[\alpha]_D^{20} = -59.5° \pm 2.5°$ (c=0.7% in chloroform).

STEP D: 11β-[4-(N-methyl-N-(3-methyl-butyl)-amino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A mixture of 52 ml of 2 N hydrochloric acid, 26 g of the product of Step C and 200 ml of methanol was stirred for one hour and was then poured into aqueous sodium bicarbonate. The mixture was extracted with ether and then methylene chloride and the combined organic phases were washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with an 92-8 toluene-ethyl acetate mixture to obtain 3.23 g of 11β-[4-(N-methyl-N-(3-methyl-butyl)-amino)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +125° \pm 3.5°$ (c=0.6% in chloroform).

Analysis: $C_{33}H_{43}NO_2$; molecular weight=485.71. Calculated: %C 81.6; %H 8.92; %N 2.88. Found: %C 81.4; %H 9.0; %N 2.7.

EXAMPLE 28

11β-[4-(N,N-dimethylaminoethylthio)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

STEP A: 4-(N,N-dimethylaminoethylthio)-bromobenzene

A solution of 23.5 g of chloroethyldimethylamine.HCl in 75 ml of ethanol was added to 160 ml of sodium hydroxide solution formed by dissolving 20 g

of sodium hydroxide pastilles in 500 ml of ethanol. A solution of 30 g of 4-bromothiophenol in 100 ml of ethanol was added to 160 ml of the said sodium hydroxide solution and the first solution was added thereto over 2 minutes at 20° C. The mixture was refluxed for 3 hours and was evaporated to dryness. Water was added to the residue and the mixture was extracted with methylene chloride. The organic phase was washed with aqueous 0.1 N sodium hydroxide solution, then with water, dried and evaporated to dryness. The residue was distilled to obtain 35.5 g of 4-(N,N-dimethylaminoethylthio)-bromobenzene boiling at 110° C. at 0.1 mm Hg.

STEP B: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminoethylthio)-phenyl]-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol

A solution of 20 g of the product of Step A in 40 ml of anhydrous tetrahydrofuran was added over 45 minutes under an inert atmosphere to a mixture of 2 g of magnesium and 15 ml of tetrahydrofuran while the temperature rose to 56° C. and the reaction was started by addition of 1,2-dibromoethane. The mixture was returned to 20° C. and was stirred at 20° C. for 45 minutes under an inert atmosphere to obtain a 1.05 M magnesium solution.

1.730 g of copper chloride were added with stirring at −20° C. under an inert atmosphere to 38 ml of the said magnesium solution and the mixture was stirred for 20 minutes. A solution of 5 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-$\Delta^{9(11)}$-estrene-17β-ol in 50 ml of anhydrous tetrahydrofuran was added to the mixture which was then stirred for 24 hours under an inert atmosphere at 20° C. and was then poured into 600 ml of iced water containing 60 g of ammonium chloride. The decanted aqueous phase was extracted with diethyl oxide containing triethylamine and the combined organic phase was washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 95-5 methylene chloride-acetone mixture to obtain 10.3 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylaminoethylthio)-phenyl]-17α-(prop-1-ynyl)-Δ^9-estrene-5α,17β-diol.

[R Spectrum: Absorption at 3600 cm^{-1} (OH); at 2240 cm^{-1} (C≡C); at 1705 and 1670 cm^{-1} (C9 and conjugated CO); at 1615 and 1490 cm^{-1} (aromatic bands).

STEP C: 11β-[4-(N,N-dimethylaminoethylthio)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A mixture of 20.6 ml of 2 N hydrochloric acid, 10.3 g of the product of Step B and 72 ml of methanol was stirred at 20° C. under an inert atmosphere for 25 minutes and was neutralized by addition of aqueous saturated sodium bicarbonate solution. 200 ml of diethyl oxide were added to the mixture and the decanted aqueous phase was extracted with diethyl oxide. The combined organic phases were washed with aqueous saturated sodium chloride solution, dried and evaporated to dryness and the residue was chromatographed over silica gel. Elution with a 9-1 methylene chloride-methanol mixture yielded 3 g of 11β-[4-(N,N-dimethylaminoethylthio)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one which after crystallization by empasting with diisopropyl oxide melted at 145° C. and had a specific rotation of $[\alpha]_D^{20} = +125° \pm 2°$ (c=1% in chloroform).

EXAMPLE 29

11β-[4-(N,N-dimethylamino)-phenyl]-21-trimethylsilyl-19-nor-17α-$\Delta^{4,9}$-pregnadiene-20-yne-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-trimethylsilyl-19-nor-17α-Δ^9-pregnene-20-yne-5α,17β-diol

A mixture of 13 ml of a 1.6 M ethyl magnesium bromide in tetrahydrofuran and 13 ml of anhydrous tetrahydrofuran was stirred for 5 minutes at 0° to 5° C. and 3.4 ml of trimethylsilyl acetylene were added thereto dropwise. The temperature was allowed to rise to 20° C. and the mixture was then stirred for 20 minutes. Then, a solution of 1.12 g of the product of Step B of Example 7 in 10 ml of anhydrous tetrahydrofuran was added dropwise to the mixture and the mixture was stirred at room temperature for 16 hours and was poured into aqueous ammonium chloride solution. The mixture was stirred at room temperature for 10 minutes and was extracted with methylene chloride. The organic phase was washed with aqueous saturated sodium chloride solution, was dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 6-4 petroleum ether-ethyl acetate mixture to obtain 680 mg of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dimethylamino)-phenyl]-21-trimethylsilyl-19-nor-17α-Δ^9-pregnene-20-yne-5α,17β-diol with a specific rotation of $[\alpha]_D^{20} = -76.5° \pm 3°$ (c=0.5% in chloroform).

STEP B: 11β-[4-(N,N-dimethylamino)-phenyl]-21-trimethylsilyl-19-nor-17α-$\Delta^{4,9}$-pregnadiene-20-yne-17β-ol-3-one

A mixture of 1 ml of 2 N hydrochloric acid, 562 mg of the product of Step A and 15 ml of methanol was stirred at room temperature for 40 minutes and was poured into aqueous sodium bicarbonate solution. The mixture was extracted with ether and the organic phase was washed with aqueous saturated sodium chloride solution, was dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 6-4 petroleum ether-ethyl acetate mixture to obtain 364 mg of 11β-[4-(N,N-dimethylamino)-phenyl]-21-trimethylsilyl-19-nor-17α-$\Delta^{4,9}$-pregnadiene-20-yne-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +97.5° \pm 3°$ (c=0.35% in $CHCl_3$).

Analysis: $C_{31}H_{41}NO_2Si$; molecular weight=487.76. Calculated: %C 76.33; %H 8.47; %N 2.87. Found: %C 76.4; %H 8.7; %N 2.8.

EXAMPLE 30

N-oxide of 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-[(prop-1-ynyl)]-$\Delta^{4,9}$-estradiene-17β-ol-3-one

A solution of 0.64 g of m-chloroperbenzoic acid in 12.8 ml of methylene chloride was added over 15 minutes at 0° to 5° C. to a solution of 1.4 g of the product of Example 23 in 28 ml of methylene chloride and the mixture was stirred at 0° to 5° C. for one hour and was then poured into aqueous 0.2 N sodium thiosulfate solution. The decanted aqueous phase was extracted with methylene chloride and the organic phase was washed with aqueous sodium bicarbonate solution, dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with an 8-2 mixture to obtain 1.28 g of N-oxide of 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-$\Delta^{4,9}$-estradiene-17β-ol-3-one. The product was dissolved in a

mixture of methylene chloride and diisopropyl oxide and the mixture was vacuum filtered to obtain 1.075 g of the said product melting at 215° C. and having a specific rotation of $[\alpha]_D^{20} = +74.5° \pm 2.5°$ (c=0.7% in $CHCl_3$).

EXAMPLE 31

Hemifumarate of 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one

A mixture of 0.378 g of fumaric acid in 4.54 ml of ethanol was added to a mixture of 1.44 g of the product of Example 23 in 2.88 ml of ethanol and the mixture was stirred at 60° C. for 30 minutes. The mixture returned to 20° C. and was stirred. The mixture was evaporated to dryness and the residue was taken up in ether. The mixture was vacuum filtered and the product was dried to obtain 1.70 g of hemifumarate of 11β-[4-(N,N-dimethylaminomethyl)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one melting at 160° C. and having a specific rotation of $[\alpha]_D^{20} = +70.5° \pm 2.5°$ (c=0.8% in $CHCl_3$).

EXAMPLE 32

11β-[4-(N,N-dipropylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one

STEP A: 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dipropylamino)-phenyl]-17α-(prop-1-ynyl)-Δ9-estrene-5α,17β-diol

A solution of 52 g of 4-bromo-N,N-dipropyl-aniline in 110 ml of tetrahydrofuran was added dropwise at 40° C. under an inert atmosphere to a mixture of 5 g of magnesium and 15 ml of anhydrous tetrahydrofuran to obtain a 1.1 M magnesium solution. A solution of 5.55 g of 3,3-[1,2-ethanediyl-bisoxy]-5α,10α-epoxy-17α-(prop-1-ynyl)-Δ9(11)-estrene-17β-ol and 200 mg of cuprous chloride was stirred at 0° to 5° C. and then 50 ml of the magnesium solution were added thereto over 15 minutes. The mixture was stirred at 20° C. for one hour and was then poured into aqueous saturated ammonium chloride solution. The mixture was extracted with ether and the organic phase was dried and evaporated to dryness. The residue was chromatographed over silica gel and was eluted with a 7-3 toluene-ethyl acetate mixture to obtain 6.3 g of 3,3-[1,2-ethanediyl-bisoxy]-11β-[4-(N,N-dipropylamino]-17α-(prop-1-ynyl)-Δ9-estrene-5α,17β-diol with a specific rotation of $[\alpha]_D^{20} = -56° \pm 2°$ (c=0.8% in $CHCl_3$).

Analysis: $C_{35}H_{49}NO_4$: molecular weight=547.75. Calculated: %C 76.74; %H 9.02; %N 2.56. Found: %C 76.6; %H 9.2; %N 2.5.

STEP B: 11β-[4-(N,N-dipropylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one

A mixture of 10 ml of 2 N hydrochloric acid, 5.83 g of the product of Step A and 80 ml of methanol was stirred at 20° C. for 50 minutes and was then neutralized by addition of N sodium hydroxide solution. The mixture was evaporated to dryness under reduced pressure and the residue was taken up in methylene chloride. The organic phase was washed with water, dried and evaporated to dryness and the residue was chromatographed over silica gel. Elution with a 3-1 toluene-ethyl acetate mixture yielded 3.81 g of 11β-[4-(N,N-dipropylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one

IR Spectrum: Absorption at 3600 cm^{-1} (OH); at 1654 cm^{-1} (C=O); at 1610-1595-1558 and 1517 cm^{-1} (Δ4,9 and aromatic bands); at 2240 cm^{-1} (C≡C).

The following products were prepared by the process of the invention using the appropriate starting materials:

(A) 11β-[4-(N-ethyl-N-methylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one melting at 174° C. and having a specific rotation of $[\alpha]_D^{20} = +149° \pm 2.5°$ (c=1% in $CHCl_3$).

(B) 11β-[N-methyl-2,3-dihydro-1H-indol-5-yl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one melting at 176° C. and having a specific rotation of $[\alpha]_D^{20} = +133° \pm 3°$ (c=0.8% in $CHCl_3$).

(C) 3-hydroxyimino-11β-[4-(N,N-dimethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol (Z isomer) melting at 260° C. and having a specific rotation of $[\alpha]_D^{20} = +141° \pm 3.5°$ (c=0.8% in $CHCl_3$) and the corresponding E isomer melting at 220° C. and having a specific rotation of $[\alpha]_D^{20} = +164° \pm 3.5°$ (c=0.8% in $CHCl_3$).

(D) N-oxide of 11β-[4-pyrrolidyl-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one melting at 220° C. and having a specific rotation of $[\alpha]_D^{20} = +88° \pm 2.5°$ (c=0.75% in $CHCl_3$)

(E) 11β-[4-(N-methyl-N-isopropylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +140° \pm 3.5°$ (c=0.5% in $CHCl_3$).

(F) N-oxide of 11β-[4-(N,N-dimethylaminoethoxy)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +60.5°$ (c=1.2% in $CHCl_3$).

(G) N-oxide of 11β-[(N-methyl)-2,3-dihydro-1H-indol-5-yl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one with a specific rotation of $[\alpha]_D^{20} = +103° \pm 2.5°$ (c=0.8% in $CHCl_3$).

(H) 11β-[4-(N-methyl-N-trimethylsilylmethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one.

(I) 11β-[4-(N-methyl-N-dimethylaminoethylamino)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one.

(J) 11β-[4-(N-methyl-piperazin-1-yl)-phenyl]-17α-(prop-1-ynyl)-Δ4,9-estradiene-17β-ol-3-one.

(K) 11β-[4-(N,N-dimethylamino)-phenyl]-17-hydroxyimino-Δ4,9-estradiene-3-one with a specific rotation of $[\alpha]_D^{20} = +207.5° \pm 3.5°$ (c=1% in $CHCl_3$).

(L) 3(E)-hydroxyimino-11β-[4-(N,N-dimethylamino)-phenyl]-17-hydroxyimino-Δ4,9-estradiene-3-one with a specific rotation of $[\alpha]_D^{20} = +195° \pm 3°$ (c=1% in $CHCl_3$) and its corresponding 3(Z) isomer with a specific rotation of $[\alpha]_D^{20} = +163° \pm 2.5°$ (c=0.6% in $CHCl_3$).

EXAMPLE 33

Tablets were prepared containing 50 mg of the product of Example 4 and sufficient excipient of talc, starch and magnesium stearate for a final tablet weight of 120 mg.

PHARMACOLOGICAL STUDY

I. Activity of products on hormonal receptors

A. Mineralcorticoidal receptor of kidneys of the rat

Male Sprague-Dawley EOPS rats weighing 140 to 160 g were surrenalectomized 4 to 8 days previously were killed and their kidneys were perfused in situ with 50 ml of a buffer (10 mM of Tris 0.25 M of Saccharose and sufficient hydrochloric acid for a pH of 7.4). The kidneys were then removed, decapsulated and homogenized at 0° C. with of a polytetrafluoroethylene-glass

Potter (1 g of tissue per 3 ml of buffer). The homogenate was centrifuged for 10 minutes at 800 g at 0° C.

After elimination of the fixation of tritiated aldosterone with glucocorticoid receptor, 21-methyl-$\Delta^{1,4,6}$-pregnatriene-20-yne-11β,17β-diol-3-one fixed only with the glucocorticoid receptor was added to the supernatant at a final concentration of 10^{-6}M. The supernatant was ultracentrifuged at 105,000 g for 60 minutes at 0° C. and aliquoits of the resulting surnageant were incubated at 0° C. with a constant concentration (T) of tritiated aldosterone in the presence of increasing concentrations (0–2500×10^{-9} M) of cold aldosterone or the cold test product. After a time (t) of incubation, the concentration of tied tritied aldosterone (B) was measured by the technique of adsorption on carbon-dextran.

B. Androgen receptor of prostate of rats

Male Sprague-Dawley EOPS rats weighing 160 to 200 g were castrated and 24 hours later, the animals were killed. The prostates were removed, weighed and homogenized at 0° C. with a polytetrafluoroethylene-glass Potter with a buffered TS solution (Tris, 10 mM, 0.25 M Saccharose, HCl-pH of 7.4) using 1 g of tissue per 5 ml of TS. The homogenate was then ultracentrifuged at 105,000 g after 60 minutes at 0° C. and aliquoits of the resulting supernatant were incubated at 0° C. for 2 hours with a constant concentration (T) of product P or 17α-methyl-$\Delta^{4,9,11}$-estratriene-17β-ol-3-one in the presence of increasing concentrations (0–1,000×10^{-9}M) of either cold P, cold testosterone or the test compound. The concentration of tied tritiated P (B) was measured for each incubate by the technique of adsorption on carbon-dextran.

C. Progestogen receptor of the uterus of rabbits

Immature rabbits weighing about 1 kg received a cutaneous application of 25 μg of estradiol and the animals were killed 5 days later. The uterus were removed, weighed and homogenized at 0° C. with a polytetrafluoroethylene-glass Potter in a buffered TS solution [Tris 10 mM, 0.25 M of Saccharose, HCl-pH of 7.4] with 1 g of tissue per 50 ml of TS. The homogenate was ultracentrifuged at 105,000 g for 90 minutes at 0° C. and aliquoits of the resulting supernatant were incubated at 0° C. for a time (t) with a constant concentration (T) of tritiated product R or 17,21-dimethyl-19-nor-$\Delta^{4,9}$-pregnadiene-3,20-dione in the presence of increasing concentrations (0 to 2500×10^{-9}M) of either cold R, cold progesterone or cold test compound. The concentration of tied tritiated R (B) was then measured for each incubate by the technique of adsorption on carbon-dextran.

D. Glucocorticoid receptor of thymus of rats

Male Sprague-Dawley EOPS rats weighing 160 to 200 g were surrenalectomized and the animals were killed 4 to 8 days later. The thymus were removed and homogenized at 0° C. in a buffered TS solution of 10 mM Tris, 0.25 M of Saccharose, 2 mM of dithiothreitol, HCl for a pH of 7.4 using a polytetrafluoroethylene-glass Potter at a rate of 1 g of tissue per 10 ml of TS. The homogenate was ultracentrifuged at 105,000 g for 90 minutes at 0° C. and aliquoats of the resulting supernatant were incubated at 0° C. for a time (t) with a constant concentration (T) of tritiated dexamethasone in the presence of an increasing concentration (0 to 2500×10^{-9}M) of either cold dexamethasone or cold test product. The concentration of tied tritiated dexamethasone (B) was measured for each incubate by the adsorption on carbon-dextran technique.

E. Estrogen receptor of uterus of mice

Immature female mice 18 to 21 days old were killed and the uterus were removed and homogenized at 0° C. with a polytetrafluoroethylene-glass Potter in a buffered TS solution consisting of 10 mM Tris, 0.25 M Saccharose, HCl for a pH of 7.4 at a rate of 1 g of tissue per 25 ml of TS. The homogenate was then ultracentrifuged at 105,000 g for 90 minutes at 0° C. and aliquoits of the resulting tritiated were incubated at 0° C. for a time (t) with a constant concentration (T) of tritied estradiol in the presence of increasing concentrations (0 to 1000×10^{-9}M) of either cold estradiol or cold test compound. The concentration of tied tritiated estradiol (B) was measured for each incubate by the technique of adsorption on carbon-dextran.

The calculation of the relative affinity of concentration (ARL) was identical for all of the above receptor tests. One traced the following two curves: the percentage of tied tritiated hormone B/T as a function of the logarithm of the cold hormone concentration and B/T as a function of the logarithm of the concentration of the cold test product. One determined the line of the equation.

$$I_{50} = \frac{\frac{B}{T}\text{ max.} + \frac{B}{T}\text{ min.}}{2}$$

B/T max. is the percentage of tied tritiated hormone for an incubation of the hormone at concentration T. B/T min. is the percentage of tied tritiated hormone for an incubation of the tritiated hormone at a concentration (T) in the presence of a large excess of cold hormone (2500×10^{-9}M).

The intersection of the I_{50} line and the curves permits one to determine the concentrations of the cold hormone of the reference (CH) and the cold test compound (CX) which inhibit by 50% the tieing of tritiated hormone with the receptor. The relative affinity of tieing (ARL) of the test product was determined by the equation:

$$ARL = 100 \times \frac{CH}{CX}$$

The results are reported in the following Tables.

Product of example	Time of incubation at 0° C.														
	Mineral corticoid			Androgen			Progestogen			Gluco-corticoid			Estrogen		
	2H	4H	24H	2H	4H	24H	2H	4H	24H	2H	4H	24H	2H	4H	24H
4	—	—		0	—	—	20	74	—	640	—	370	265	0	—	—
17	—	—		0	—	—	46	81	—	331	—	279	233	0	—	—
14	—	—		—	—	—	0	41	—	230	—	46	94	0	—	—
8	—	—		0	—	—	14,7	81	—	366	—	212	167	0	—	—
10	—	—		0	—	—	32	78	—	463	—	254	272	0	—	—
11	—	—		0	—	—	9,8	6,3	—	6,3	—	9	14	0	—	—
16	—	—		1,7	—	—	29	129	—	166	—	283	259	0	—	—

-continued

Product of example	Time of incubation at 0° C.														
	Mineral corticoid			Androgen			Progestogen			Gluco-corticoid			Estrogen		
	2H	4H	24H	2H	4H	24H	2H	4H	24H	2H	4H	24H	2H	4H	24H
12	—	—	0	—	—	2.8	0.6	—	0.4	—	5.3	6.2	0	—	—
6	—	—	0.8	—	—	7.3	10	—	4.3	—	171	118	0	—	—
20	—	—	—	—	—	2.2	1.1	—	2.5	—	7.8	5	0	—	—
22	—	—	0.3	—	—	8	175	—	843	—	175	221	0	—	—
16	—	—	0	—	—	4.6	15.2	—	38	—	79	104	0	—	—

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CONCLUSION

The tested compounds and especially those of Examples 4,10,16,17 and 22 present a very remarkable affinity for glucocorticoid and progestogen receptors as well as a slight affinity for androgen receptors. On the contrary, the products do not have any activity for mineralcorticoid and estrogen receptors. These results lead to the conclusion that the products present an agonist or antagonistic activity to glucocorticoids, progestogens and androgens.

II Anti-inflammatory Activity

The anti-inflammatory activity of the compound of Example 4 was determined by the classical granuloma test by a modification of the Meier et al test [Experientia. Vol. 6 (1950), p. 469] in which normal female Wistar rats weighing 100 to 110 g received an implantation of 2 pellets of cotton weighing 10 mg each under the thorax skin. The subcutaneous treatment which began immediately after the implantation for 2 days was 2 injections per day. 16 hours after the last injection, the animals were killed and the pellets together with the granuloma tissue formed were weighed in the fresh state and after 16 hours at 60° C. The weight of the granuloma was obtained by subtracting the initial weight of the cotton. The thymus was also removed and weighed to determine the thymolytic activity of the test product.

At a subcutaneous dose of 50 mg/kg, the product of Example 4 did not show any glucocorticoidal anti-inflammatory activity or thymolytic activity.

III Antiglucocorticoidal Activity

The test used was that of Daune et al. [Molecular Pharmacology, Vol. 13 (1977), p. 948–955] entitled "The relationship between glucocorticoid structure and effects upon thymocytes" for mice thymocytes. The thymocytes of surrenalectomized rats were incubated at 37° C. for 3 hours in a nutritive medium containing 5×10^{-8} M of dexamethasone in the presence or absence of the test compound at different concentrations. Tritiated uridine was added and incubation was continued for one hour. The incubates were cooled and treated with a 5% trifluoroacetic acid solution and the mixture was filtered with Whatman GF/A paper. The filter was washed 3 times with a 5% trifluoroacetic acid solution and retained radioactivity on the filter was determined. Glucocorticoids and especially dexamethasone provoked a lessening of incorporation of tritiateduridine and the tested compounds, especially those of Examples 4,6,8,10,11,14,16,20 and 22, opposed this effect as can be seen from the following Table.

Product of Example	$5 \cdot 10^{-8}$ Dexamethasone + Product tested	% of inhibition of effect of Dexamethasone
4	10^{-8} M	30
	10^{-7} M	70
	10^{-6} M	90
14	10^{-8} M	18
	10^{-7} M	57
	10^{-6} M	*
8	10^{-8} M	22
	10^{-7} M	53
	10^{-6} M	*
10	10^{-8} M	57
	10^{-7} M	85
	10^{-6} M	*
11	10^{-8} M	14
	10^{-7} M	34
	10^{-6} M	75
16	10^{-8} M	28
	10^{-7} M	60
	10^{-6} M	99
6	10^{-8} M	5
	10^{-7} M	15
	10^{-6} M	83
20	10^{-8} M	4
	10^{-7} M	21
	10^{-6} M	90
22	10^{-8} M	16
	10^{-7} M	69
	10^{-6} M	*

*A dose of 10^{-6} M inhibited totally the effect of dexamethasone

CONCLUSION

The products of the invention used alone do not provoke any effect of the glucocorticoid type and the tested products present a very remarkable antiglucocorticoid activity and are devoid of any glucocorticoid activity.

IV Progestomimetic And Anti-Progestomimetic Activity

(a) Groups of immature female rabbits weighing about 1 kg had administered to them sub-cutaneously from day 1 to day 5, 5 μg of estradiol. The product tested is afterward administered orally from day 8 to day 11 in a volume of 0.5 cm^3 of water containing 0.5% of carboxymethyl cellulose and 0.2% of Tween. On day 12 the rabbits were sacrificed, their uteruses were retained and fixed in Bouin's solution and histologically studied.

The changes in the uterine endometrium were noted according to the method of McPhail. Only superior results or those equal to two units of McPhail were considered significant.

The following results were obtained.