

DIVISIÓN DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No 03-018359

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION**

FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **544** DE

FECHA **30 DE SEPTIEMBRE DE 2004** EL TÉRMINO HÁBIL SEÑALADO POR

LA LEY EXPIRA EL **29 DE DICIEMBRE DEL 2004**

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ☐ _ _ _ _ _

NO ☒ _ _ X _ _

DL 209

United States Patent [19]

Lenz

[11] 4,389,345

[45] Jun. 21, 1983

[54] 3-OXOESTRA-17-ACETONITRILE AND
UNSATURATED ANALOGS

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[21] Appl. No.: 310,204

[22] Filed: Oct. 9, 1981

[51] Int. Cl.³ C07J 7/00

[52] U.S. Cl. 260/397.1; 260/397.3;
260/397.5

[58] Field of Search 260/397.1, 397.3, 397.5

[56]

References Cited

U.S. PATENT DOCUMENTS

3,960,842 6/1976 Haffer et al. 260/239.55-C

OTHER PUBLICATIONS

Pettit et al., J. Org. Chem. 1971, 36(21) pp. 3207-3211,
as found in Chem. Abstract (1971) vol. 75, 151, 969x.

Primary Examiner—Elbert L. Roberts

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[57]

ABSTRACT

This invention relates to cyano steroids of formula I.
These compounds exhibit progestational activity.

15 Claims, No Drawings

3-OXOESTRA-17-ACETONITRILE AND UNSATURATED ANALOGS

BACKGROUND OF THE INVENTION

The invention relates to certain novel cyano steroids. In particular, the invention relates to novel cyano steroids of formula 1 which exhibit progestational activity.

Compounds, particularly steroids, which exhibit progestational activity are widely known in the art. Both naturally occurring and synthetic compounds of this type are well known, for example, progesterone and ethisterone respectively. Such compounds are useful in treating functional uterine bleeding, dysmenorrhea, and endometriosis. For a detailed discussion of progestins see, for example, Goodman and Gilman, *The Pharmacological Basis of Therapeutics* 4th pps. 1550-1557 (1970). See also, for example, U.S. Pat. No. 3,812,166.

PRIOR ART

Steroids with progestational activity are widely known as discussed above. In particular certain cyanosteroids are known. For example, 3-(acetyloxy)pregna-5,17(20)-diene-21-nitrile is described in Chem. Abstracts 618365h, 3-oxo-pregn-4-ene-21-nitrile is described in Chem. Abstracts 75151969x, and 3-(acetyloxy)pregn-5-ene-21-nitrile is described in Index Chem. 1485996.

SUMMARY OF THE INVENTION

The invention particularly provides a compound according to Formula I:

wherein R₁ is:

- (a) hydrogen;
- (b) H₂; or
- (c) COOR₂;

wherein R₂ is:

- (a) hydrogen; or
- (b) alkyl of one to six carbon atoms, inclusive; or
- (c) aralkyl of four to thirteen carbon atoms, inclusive;

wherein R₃ is:

- (a) oxo;
- (b) =NOH; or
- (c) -OR₄;
- (d) -OC=O(R₄)

wherein R₄ is:

- (a) hydrogen; or
- (b) alkyl of one to six carbon atoms, inclusive;

with the proviso that R₁ may not be hydrogen or H₂ when R₃ is oxo or when R₃ is -OAcetyl.

Examples of alkyl of one to six carbon atoms, inclusive, are methyl, ethyl, propyl, butyl, pentyl and hexyl and the isomeric forms thereof.

Examples of aralkyl of four to thirteen carbon atoms, inclusive, are where the alkyl portion is from one to six carbon atoms inclusive as described above and the aryl portion is a cyclic compound from 3 to 7 atoms inclusive; examples include cyclopropyl methyl, cyclopropyl ethyl, cyclopropyl propyl, cyclopropyl butyl, cyclopropyl pentyl, cyclopropyl hexyl, cyclobutyl methyl, cyclobutyl ethyl, cyclobutyl propyl, cyclobutyl butyl, cyclobutyl pentyl, cyclopropyl hexyl, cyclopentyl methyl, cyclopentyl ethyl, cyclopentyl propyl, cyclopentyl butyl, cyclopentyl pentyl, cyclopentyl hexyl, cyclohexyl methyl, cyclohexyl ethyl, cyclohexyl propyl, cyclohexyl butyl, cyclohexyl pentyl, cyclohexyl hexyl, cycloheptyl methyl, cycloheptyl ethyl, cy-

cloheptyl propyl, cycloheptyl butyl, cycloheptyl pentyl, cycloheptyl hexyl, benzyl methyl, benzyl ethyl, benzyl propyl, benzyl butyl, benzyl pentyl, benzyl hexyl, and the other saturated, unsaturated, partially saturated and isomeric forms thereof.

The test procedure used to determine progestational activity is as follows:

Immature, intact female rabbits, are primed with 5 micrograms of estradiol-17- β daily for 6 days. The uterus is the organ involved in this exam with histological examination of the uterine endometrium being performed. An initial screening dose of the test compound of 1/mg/kg is administered subcutaneously, buccally or intragastrically with the dosage adjusted as necessary. All test compounds are run against progesterone as a standard.

The degree of arborization of the luminal epithelium of the uterus is graded from +1 to +4. An average rating of +2 represents minimal activity (produced by progesterone subcutaneously at 0.05 mg/day) while an average rating of +3.5 to +4.0 represents maximal activity (produced by progesterone subcutaneously at 0.1 mg/day). Unless stated to the contrary, potency estimates will be made by comparing doses of the standard and test compound that produce minimal activity.

Arborization (proliferation) of glandular epithelium in estrogen primed rabbits is brought about by progesterone. Progesterone, or a functional corpus luteum, is a factor in normal uterine development in the menstrual cycle and maintenance of pregnancy. Development and function of mammary tissue is also influenced by progestins. Concurrently with this test, endocrinal carbonic anhydrase is determined, an increase in which indicates progestational activity, as shown by Miyake, et al, *Endocrinology*, 63 816 (1958).

By virtue of this progestational activity the compounds of formula I are useful in treating functional uterine bleeding, dysmenorrhea and endometriosis. The compounds can be administered in such oral unit dosage forms such as tablets, capsules, pills, powders, or granules. They also may be administered rectally, vaginally in such forms as suppositories; they may also be introduced in the form of eye drops, interparenterally, subcutaneously, or intramuscularly, using forms known to the pharmaceutical art. In general, the preferred form of administration is orally.

An effective but non-toxic quantity of the compound is employed in treatment. The dosage regimen for preventing or treating symptoms by the compounds of this invention is selected in accordance with a variety of factors including the type, age, weight, sex, and medical condition of the mammal, the severity of the symptoms, the route of administration and the particular compound employed.

Initial dosages of the compounds of the invention are ordinarily in the area of 1 mg/kg up to at least 50 mg/kg orally. When other forms of administration are employed, equivalent doses are administered. When dosages beyond 50 mg/kg are employed, care should be taken with each subsequent dose to monitor possible undesirable effects.

The compounds of this invention may be administered in a suitable hydrated form.

The compounds of the invention are prepared according to the following general procedures.

To a solution of a sodium salt of diethylcyanomethylene phosphonate in a suitable solvent like tetrahydrofu-

ran or 1,2-dimethoxyethane is added a 19-norandrostene-3,17-dione with the 3 ketone suitably protected as in enol ether, a dimethoxy ketal or an ethylenedioxy ketal. After a suitable contact time, the reaction mixture is poured into water and the protected 7 cyanomethylene steroid collected. The protecting group is removed by warming an aqueous alcohol preferably methanol or ethanol, with an acid such as citric, p-toluenesulfonic or hydrochloric. Upon regeneration of the 3-ketone, the steroid is isolated by dilution with water. For example, one part of the 3-enol ether of 19-nor-androstene-3,17-dione (C. DJERASSI, et al *J. AMER. CHEM. SOC.* 76, 4092 (1954)) in 2.5 parts of 1,2-dimethoxyethane is added to 40 parts of a solution of the sodium salt of diethylcyanomethylene phosphonate in the same solvent. After heating to reflux for an appropriate time, the resultant mixture is poured into about 500 parts of water and the enol ether collected and dried. One part of the enol ether may be dissolved by heating in 200 parts of methanol and 25 parts of distilled water. One part of p-toluenesulfonic acid has been added. After about 15 minutes the solution is diluted with water and then the deprotected ketone is obtained.

To prepare 3-hydroxy steroids the invention, a solution of the sodium salt of diethylcyanomethylene phosphonate and a suitable solvent such as tetrahydrofuran or 1,2-dimethoxyethane, is added a 3-hydroxy-19-norandrost-5-ene-17-ketone with the 3-alcohol suitably protected as a tetrahydropyranyl ether, a trialkylsilyl ether or a tetrahydrofuran ether. After a suitable contact time, the reaction mixture is poured into water and the protected 7-cyanomethylene steroid is collected. The protecting group may be removed by treatment with an acid such as p-toluenesulfonic, hydrochloric or citric, in an aqueous alcohol, or with a fluoride anion if the protecting group is trialkylsilyl. The resultant 3-hydroxy-5-en-steroids may be oxidized to the conjugated enone by means of the OPPENAUER reaction. (For example see U.S. Pat. No. 3,597,418).

To prepare 3- β hydroxy steroids of the invention, a mixture of 3 β -hydroxy-19-nor-androst-5-ene-17-ketone with the hydroxyl group protected with an acyl or aroyl group is added 4 parts of acetic acid, 4 parts of benzyl cyanoacetate and 3 parts of ammonium acetate and 15 parts of benzene. After a suitable reflux period, the mixture is diluted with additional solvent and the mixture washed with water. After drying the organic solution with a suitable drying agent, such as sodium sulfate, magnesium sulfate, or calcium chloride, the solvent is removed and the resultant cyano acrylate steroid crystalized from a suitable solvent. After dilution with additional solvent, the mixture is washed with water the organic layer dried with sodium sulfate or other appropriate material and evaporated.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The invention can be more fully understood by the following examples. The example compound structures are represented on Charts A through E as well as the schematic order of production.

EXAMPLE 1

3-Ethoxy-19-Norprega-3,5,17(20)-Triene-21-Nitrile

To a suspension of 3.5 parts of sodium hydride and 25 parts of dry 1,2-dimethoxyethane is added 14.5 parts of diethylcyanomethylene phosphonate in 15 parts of the same solvent. After hydrogen evolution ceases, 20 parts

of the enol ether of 19-norandrostenedione in 50 parts of warm 1,2 dimethoxyethane is added. The solution is refluxed for 2 hours and poured into 500 parts of distilled water. After crystallization is complete, the title compound is filtered and air dried.

EXAMPLE 2

3-Oxo-19-Norpregna-4,17(20)-Diene-Nitrile

One part of the title compound of Example 1 is dissolved by heating in 200 parts of methanol and 25 parts of distilled water. Then one part of p-toluenesulfonic acid monohydrate is added. After 15 minutes the solution is poured into water and the title compound is collected which has a melting point of 147 to 149.5 degrees centigrade.

EXAMPLE 3

3-Hydroxy-19-Norpregna-5,17(20)-Diene-21-Nitrile

To a suspension of 1.25 parts of sodium hydride and 50 parts of tetrahydrofuran is added 9.3 parts of diethylcyanomethylene phosphonate is 25 parts of the same solvent. After hydrogen evolution ceases, 5.5 parts of the tetrahydropyranyl ether of 19-nor-dehydroisoandrosterone in 25 parts of the same solvent is added. After standing at room temperature for 16 hours, the reaction mixture is diluted with 350 parts of water and the precipitated product collected.

The crude product is then suspended in 300 parts of ethanol and 1.5 parts of p-toluenesulfonic acid monohydrate is added. After stirring for 16 hours, the solution is diluted with 800 parts of water. The title product is collected having a melting point of 104° to 108° C. The title product may then be dissolved in 100 parts of toluene and 2 parts of N-methyl-4-piperidone and 2 parts of aluminum isopropoxide added. After refluxing for 3 hours the reacting mixture is cooled and washed with hydrochloric acid. The toluene solution is dried over sodium sulfate and evaporated to yield the title compound of Example 2 after recrystallization from an acetone water solvent system.

EXAMPLE 4

3-Acetyloxy-19-Norpregna-5,17(20)-Diene-21-Nitrile

To a solution of 3 parts of sodium diethylcyanomethylene phosphonate in 25 parts of tetrahydrofuran is added 1 part of 19-nor-dehydroisoandrosterone acetate. After stirring at room temperature for 16 hours, the solution is diluted with 225 parts of distilled water and the title compound is collected which has a melting point of 187° to 194° C. The title compound may then be dissolved in 20 parts of tetrahydrofuran and treated with 1 part of potassium carbonate and 3 parts of water. After stirring for 16 hours the mixture may be diluted with 150 parts of water and the title product of Example 3 may be obtained.

EXAMPLE 5

3-Methoxy-19-Norprega-2,5(10),17(20)-Triene-21-Nitrile

To a solution of 913 parts of sodium diethylcyanomethylene phosphonate and 100 parts of tetrahydrofuran is added 5 parts of 1,4-dihydroestrone in 125 parts of the same solvent. After stirring for 16 hours, the solution is diluted with 1,800 parts of water and the crude product is collected. Recrystallization from

methylene chloride ethanol solvent system gives the title product which has a melting point of 164.5° C.

EXAMPLE 6

3-Oxo-19-Norpregna-5(10),17(20)-Diene-21-Nitrile

One part of the title compound of Example 5 is suspended in 95 parts of methanol and 0.7 parts of oxalic acid and 10 parts of water is added. After stirring for 1 hour, the solution is diluted with 400 parts of water to yield the title compound having a melting point of 144.5 degrees to 147° C.

EXAMPLE 7

3-Oxo-19-Norpregna-4,9,17(20)-Triene-21-Nitrile

To 1 part of the title compound of Example 6 dissolved in 25 parts of dried pyridine is added 1.2 parts of pyrrolidine hydrotribromide. After stirring for 48 hours, the majority of the solvent is evaporated and 50 parts of methylene chloride is added. The solution is washed successively with 50 parts of a 5 percent hydrochloric acid solution and 5 percent bicarbonate solution and dried with sodium sulfate. After treatment with decolorizing carbon, the solvent is removed and the residue chromatographed on silica using a mixture of 1 part ethyl acetate and 4 parts toluene as a solvent system. After removal of the solvents, the residue is crystallized from a methanol water solvent system to give the title product which has a melting point of 140.5 degrees to 143° C.

EXAMPLE 8

3-Oxo-19-Norpregna-4,9,11,17(20)-Tetraene-21-Nitrile

1 part of acetyl chloride is added to 60 parts of anhydrous methanol at 0° C. Then 1 part of the title compound of Example 7 is added and goes into solution. After one-half hour the mixture is diluted with 50 parts of water to give the 5(10),9(11)-dienone having a melting point of 150° to 155° C. One part of the deconjugated compound is dissolved in 50 parts of dioxane and 1.8 parts of recrystallized dichlorodicyanobenzoquinone is added. After stirring at room temperature for 22 hours, the precipitated hydroquinone is filtered and the solvent evaporated. Residue is dissolved in 75 parts of methylene chloride and washed with 100 parts of 2.5 percent sodium bisulfite solution. After separation the organic layer is dried with sodium sulfate and the solvent evaporated. The residue is chromatographed on silica using 15 parts of ethyl acetate and 85 parts of methylene chloride to yield the title product having a melting point 159.5° to 160.5° C. after recrystallization from a methylene chloride methanol solvent system.

EXAMPLE 9

Phenylmethyl

3-(Acetyloxy)-20-Cyano-19-Norpregna-5,17(20)-Dien-21-Oate

3.8 parts of 19-nor-dehydroisoandrosterone acetate in a mixture of 60 parts of benzene, 50 parts of acetic acid, 4.2 parts of benzylcyanoacetate and 3 parts of ammonium acetate is refluxed for 16 hours. After cooling, the mixture is diluted with 250 parts of toluene and washed 3 times with water. After drying with sodium sulfate, the solvent is evaporated and the residue crystallized from methanol to yield the title compound having a melting point of 155° C.

EXAMPLE 10

Phenylmethyl

20-Cyano-3-Hydroxy-19-Norpregna-5,17(20)-Diene-21-Oate

5 parts of the title compound of Example 9 is transesterified with 125 parts of ethanol and 125 parts of toluene containing 2 parts of p-toluenesulfonic acid monohydrate. After refluxing for 12 hours, 2 parts of pyridine is added and the solvents removed. Residue is crystallized from methanol water to yield the title product which has a melting point of 104° to 109° C.

EXAMPLE 11

Phenylmethyl

20-Cyano-3-Oxo-19-Norpregna-4,17(20)-Dien-21-Oate

The title compound of Example 10 is oxidized to form the title compound using the modified Oppenauer oxidation described in the preparation of the title compound in Example 2. Title compound has a melting point of 142° to 140° C. like those used in Examples 3 and 4. The title compound may then be hydrogenated in tetrahydrofuran using palladium on strontium carbonate as a catalyst whereby the benzyl group is cleaved and decarboxylation occurs to yield the title compound of Example 2.

EXAMPLE 12

3-Oxo-19-Norpregna-4,17(20)-Diene-21-Nitrile Oxime

1 part of the title compound of Example 11 is suspended in 10 parts of ethanol and then 0.3 parts of hydroxylamine hydrochloride and 5 parts of pyridine is added. After stirring at room temperature for 2 hours, the solution is diluted with water to yield the title compound which has a melting point of 141° C. with decomposition.

EXAMPLE 13

3-Oxo-19-Norpregna-4-Ene-21-Nitrile

To a solution of 22 parts of sodium diethylcyanomethylene phosphonate and 180 parts of tetrahydrofuran, is added 20 parts of the 3-dimethyl ketal of 19-nor-5(10)-androstene-3,17-dione in 200 parts of tetrahydrofuran. After stirring at room temperature for 21 hours, the mixture is poured in water and the granular precipitate collected. The solid is dissolved in 400 parts of methylene chloride treated with a decolorizing charcoal and filtered using filter acid. The solution is diluted with 400 parts of ethanol and the volume reduced to 200 parts. The cyanomethylene ketal which crystallizes upon scratching has a melting point of 145° to 148° C.

1 part of the cyanomethylene ketal is suspended in 40 parts of methanol and 2.9 parts of magnesium is added. The exothermic reaction is moderated with intermittent cooling with a water bath and stirred for 4 hours. Then 25 parts of citric acid in 100 parts of water is added to the gelatinous mixture and the resultant solution is extracted with 200 parts of chloroform in 3 portions. After drying with sodium sulfate, the solvent is removed and the residue chromatographed on silica with 5 parts of ethyl acetate and 95 parts of toluene as a solvent system. The resultant reduced ketal is dissolved in 20 parts of 2 N aqueous hydrochloric acid. After 2 hours the layers are separated and the organic layer washed with 20 parts of 5 percent sodium bicarbonate. After drying over sodium sulfate, the solvent is removed and the

residue crystallized from an ether and petroleum ether solvent system to yield the title compound which has a melting point of 115° to 118° C.

CHART A

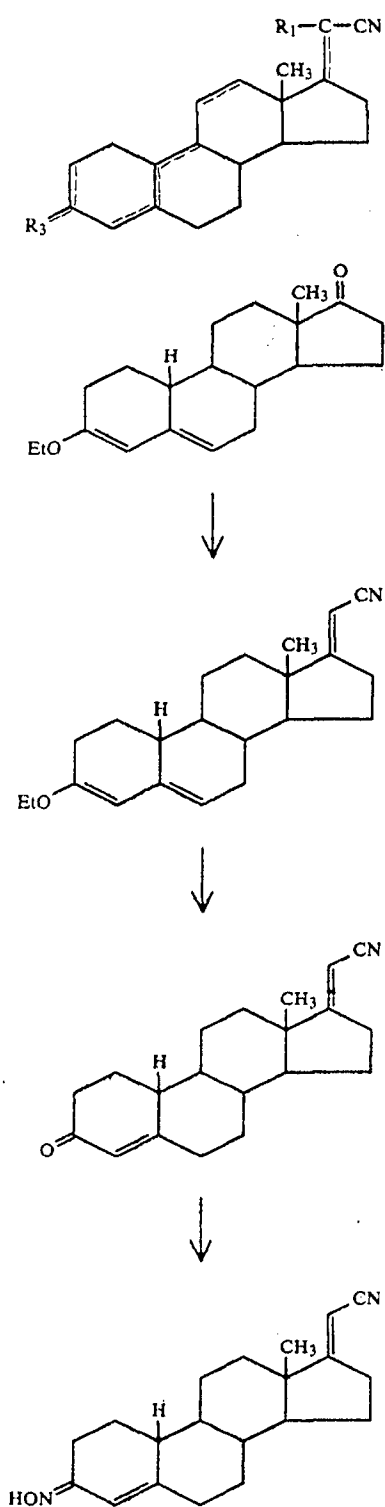


CHART B

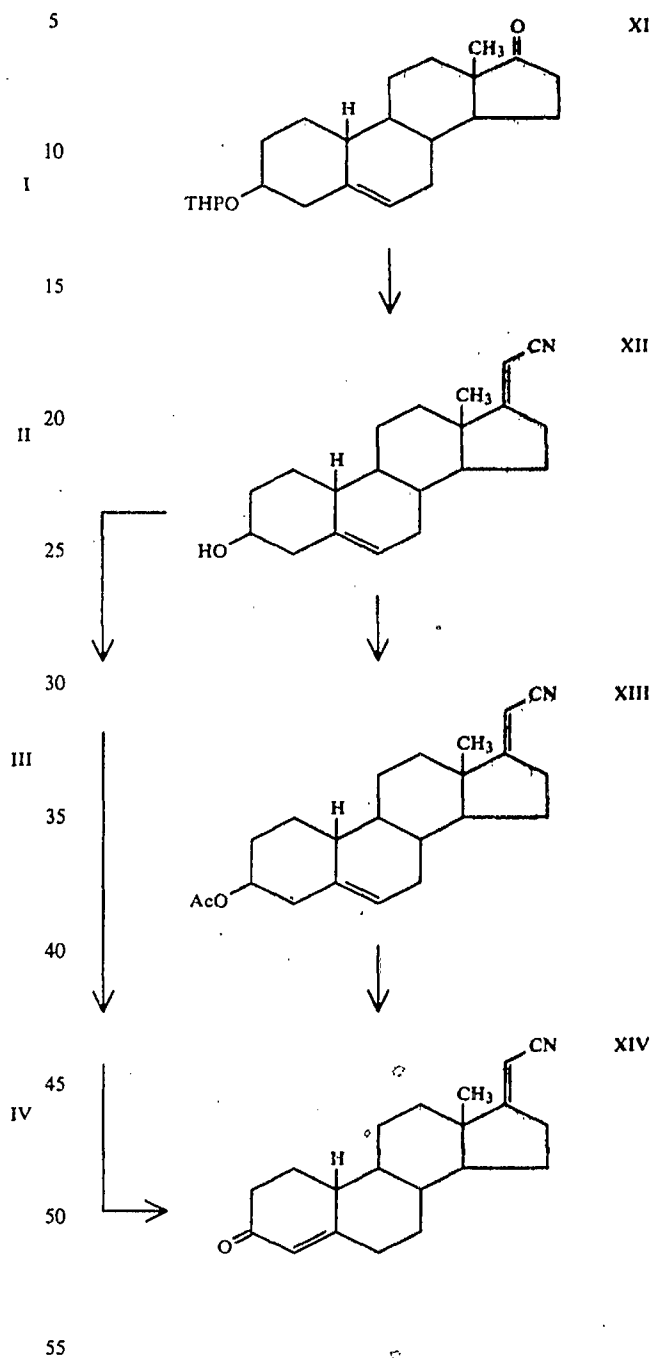
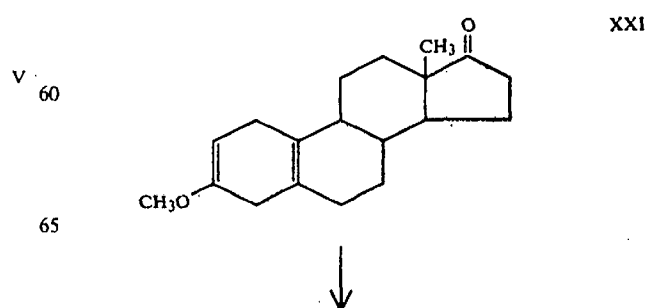


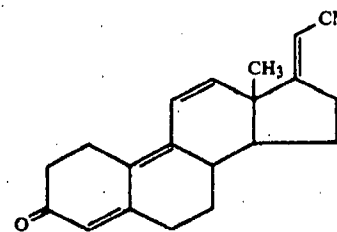
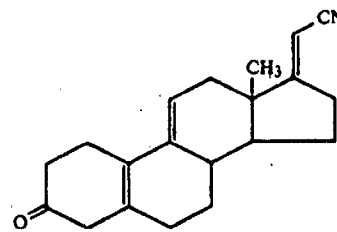
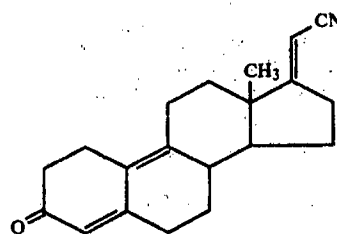
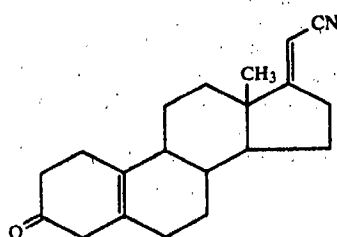
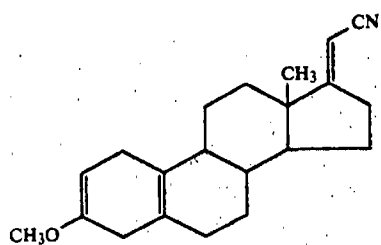
CHART C



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CHART C



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CHART D.

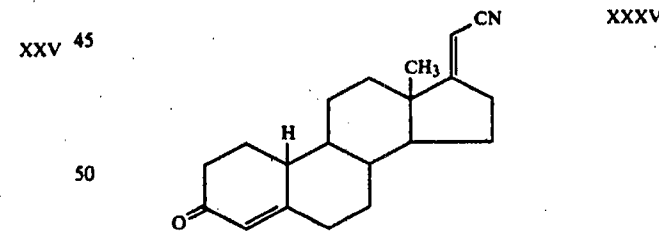
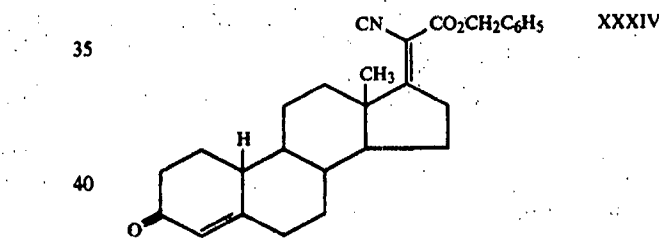
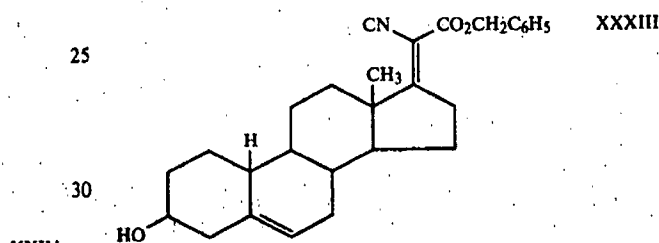
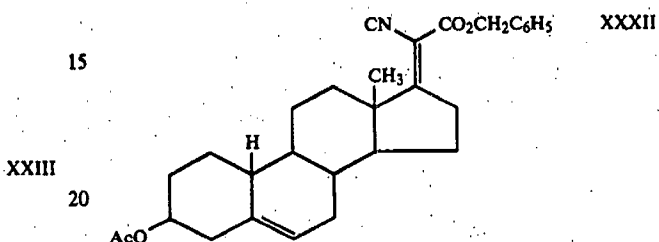
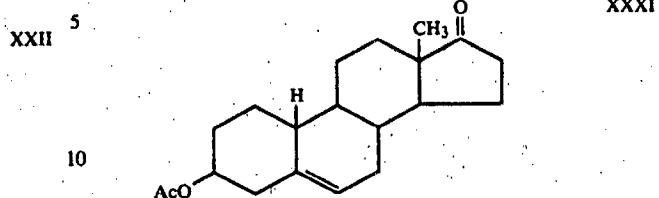
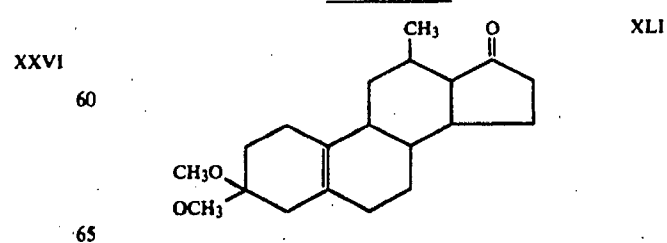


CHART E

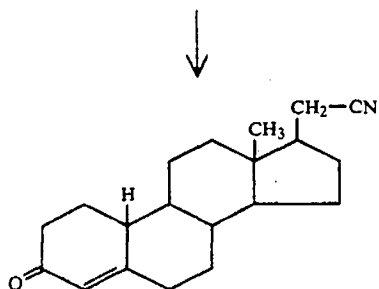
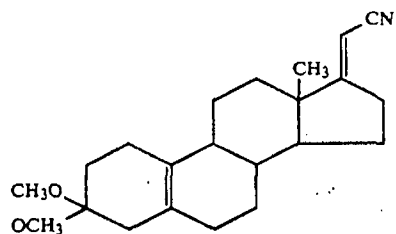


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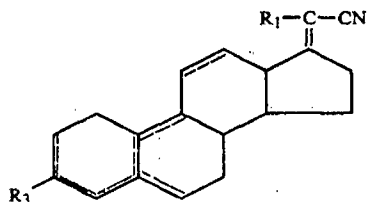
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-continued
CHART E



I claim:

1. A compound of the formula:



wherein R₁ is:

(a) hydrogen;

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(b) phenyl alkyl carboxylic acid ester, the alkyl portion having 1 to 6 carbon atoms inclusive;

wherein R₃ is

XLII

- (a) oxo
- (b) =NOH;
- (c) —OR₄; or
- (d) —OC=O(R₄)

wherein R₄ is

- (a) hydrogen; or
- (b) alkyl of 1 to 6 carbon atoms inclusive.

2. 3-Oxo-19-norpregna-4,17(20)-diene-21-nitrile, a compound according to claim 1.

3. Phenylmethyl-20-cyano-3-oxo-19-norpregna-4,17(20)-dien-21-oate, a compound according to claim 1.

XLIII

4. 3-Oxo-19-norpregna-4,9,17(20)-triene-21-nitrile, a compound according to claim 1.

5. 3-Oxo-19-norpregna-5(10),17(20)-diene-21-nitrile, a compound according to claim 1.

6. 3-Oxo-19-norpregna-4,9,11,17(20)-tetraene-21-nitrile, a compound according to claim 1.

7. A compound according to claim 1 wherein R₃ is =NOH.

8. 3-Oxo-19-norpregna-4,17(20)-diene-21-nitrile oxime, a compound according to claim 7.

9. A compound according to claim 1 wherein R₃ is —OR₄.

10. 3-Ethoxy-19-norpregna-3,5,17(20)-triene-21-nitrile, a compound according to claim 9.

11. Phenylmethyl-20-cyano-3β-hydroxy-19-norpregna-1,5,17(20)-dien-21-oate, a compound according to claim 9.

12. 3-methoxy-19-norpregna-2,5(10),17(20)-triene-21-nitrile, a compound according to claim 9.

13. 3β-hydroxy-19-norpregna-5,17(20)-diene-21-nitrile, a compound according to claim 9.

14. A compound according to claim 1 wherein R₃ is —OC=O(R₄).

15. 3β-(acetyloxy)-19-norpregna-5,17(20)-diene-21-nitrile, a compound according to claim 14.

* * * * *

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D2 216

United States Patent Office

3,146,239

Patented Aug. 25, 1964

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3,146,239

4-HALO-19-NOR-PROGESTERONE

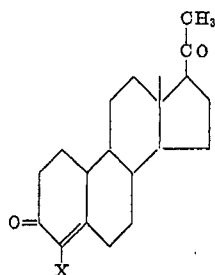
Howard J. Ringold, Octavio Mancera, and Enrique Batres, Mexico City, Mexico, assignors, by mesne assignments, to Syntex Corporation, a corporation of Panama No Drawing. Filed Sept. 22, 1958, Ser. No. 762,268 Claims priority, application Mexico Sept. 23, 1957 3 Claims. (Cl. 260—397.3)

The present invention relates to novel cyclopentanophenanthrene derivatives.

More particularly the present invention relates to 4-chloro or 4-bromo-19-nor-progesterone. The novel compounds of the present invention are active progestational type hormones.

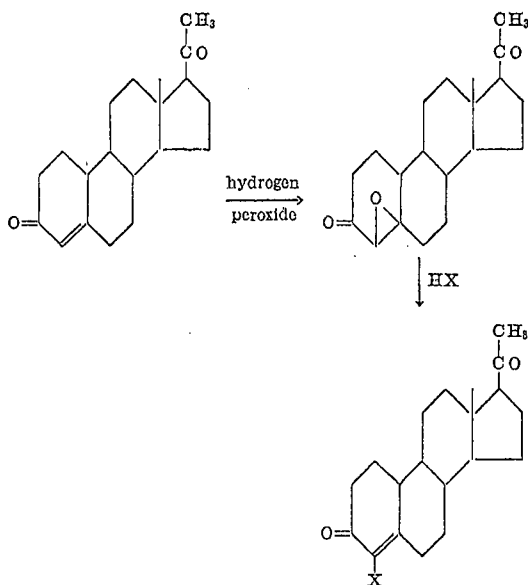
In accordance with the present invention it has been discovered that the novel 4-chloro or 4-bromo-19-nor- Δ^4 -pregnen-3,20-diones may be prepared by epoxidizing the double bond of 19-nor-progesterone followed by the opening of the epoxide ring with hydrochloric or hydrobromic acid.

The novel compounds of the present invention have the following formula:



In the above formula X represents chlorine or bromine.

The above novel compounds are prepared by a process illustrated by the following formula:



In the above equation X represents bromine or chlorine as heretofore.

In practicing the process above set forth 19-nor-progesterone is reacted with hydrogen peroxide in the presence of a base such as sodium hydroxide. The 4 β , 5 β -oxido-19-nor-pregnan-3,20-dione thus formed is then reacted with concentrated hydrochloric or hydrobromic acid to form the desired 4-chloro or 4-bromo-19-nor-progesterone.

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The following specific examples serve to illustrate but are not intended to limit the present invention.

Example I

A solution of 0.8 g. of 19-nor-progesterone in 100 cc. of methanol was cooled to 0° C. and slowly mixed with stirring with 3.5 cc. of 33% hydrogen peroxide solution and then with 3.5 cc. of 10% aqueous sodium hydroxide solution, while the temperature of the mixture was maintained below 0° C. The mixture was stirred at this temperature for one hour further, filtered and diluted with saturated aqueous sodium chloride solution. The product was extracted with three portions of ethyl acetate and the extract was washed with water, dried over anhydrous sodium sulfate, filtered and evaporated to dryness. There was thus obtained the crude 4 β , 5 β -oxido-19-nor-pregnan-3,20-dione. Chromatographic purification afforded the analytical sample.

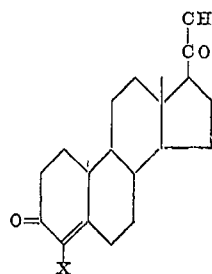
0.8 g. of the above crude epoxide was dissolved in 40 cc. of acetone, the solution was cooled in an ice bath and then there was added 1.2 cc. of concentrated hydrochloric acid. The mixture was kept standing for one hour at room temperature and then it was poured into saturated aqueous sodium chloride solution; after cooling, the crystalline precipitate was collected by filtration. There was thus obtained the desired 4-chloro-19-nor-progesterone in crude form, M.P. 156–161° C. Several recrystallizations from acetone-hexane produced the pure substance which melted between 175 and 177° C.; $[\alpha]_D^{20} +127^\circ$ (chloroform); ultraviolet absorption λ max. 256 $m\mu$ log E 4.11.

Example II

0.5 g. of the crude 4 β , 5 β -oxido-19-nor-pregnan-3,20-dione, obtained in accordance with the previous example, was dissolved in 30 cc. of acetone, cooled to 0° C. and then treated with 1.2 cc. of constant boiling aqueous hydrobromic acid (approximately 48%), following the method described in such example for the treatment with hydrochloric acid. There was thus obtained 4-bromo-19-nor-progesterone.

We claim:

1. A compound of the following formula:



wherein X is selected from the group consisting of chlorine and bromine.

2. 4-chloro-19-nor-progesterone.
3. 4-bromo-19-nor-progesterone.

References Cited in the file of this patent

UNITED STATES PATENTS

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| 2,842,571 | Camerino et al. | July 8, 1958 |
| 2,933,510 | Julian et al. | Apr. 19, 1960 |

OTHER REFERENCES

- "Journal Chemical Society," 1956, pages 627–9, Kirk et al.
- Camerino et al.: Formaco (Pavis), Ed. Sci., vol 13, pp. 52–63 (1958), or Chem. Abstracts, vol. 52, par. 13, 769(c).

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3,661,940

DERIVATIVES OF 21-METHYL-19-NORPREGNANES

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No Drawing. Filed Apr. 13, 1970, Ser. No. 28,554

Int. Cl. C07c 169/34

U.S. Cl. 260—397.3

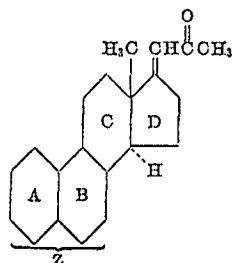
16 Claims

ABSTRACT OF THE DISCLOSURE

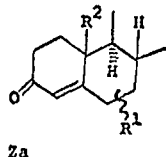
The compounds are 21-methyl-19-norpregnane derivatives bearing a double bond in the 17(20)-position and a keto-group in the 21-position, e.g., 21-methyl-19-nor-4, 17(20)-pregnadiene-3,21-dione. Said compounds are useful as pharmaceutical agents, and may be obtained by treatment of a 17-alpha-propadienyl, 17-beta-hydroxy-substituted steroidal compound, e.g. with a protonating agent.

This invention relates to steroidal compounds and more particularly to 21-methyl-19-norpregnane derivatives. This invention also relates to the preparation of such compounds and intermediates thereof.

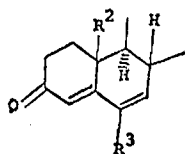
According to this invention, compounds are provided having the formula (Compounds I)



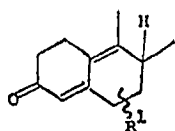
wherein Z embracing rings A and B and the substituents thereon represents



Za



Zb



Zc

or

in which

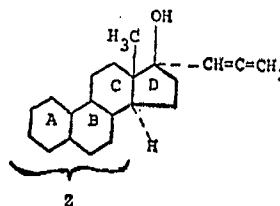
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R¹ represents hydrogen, a 6α-methyl group or a 7α-methyl group,

R² represents hydrogen or a methyl group, and

R³ represents hydrogen, halogen having an atomic weight of from 19 to 36, i.e. fluoro or chloro, or a methyl group.

According to this invention, Compounds I are provided by acidic treatment (Process a) of a Compound II, i.e. a corresponding 17α-propadienyl-17β-hydroxy steroidal compound:



II'

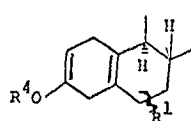
Such acidic treatment (Process a) may be carried out employing as the "acidic" source a strong protonating agent in the presence of hydroxy, (lower) acyloxy or (lower) alkoxy anion, in a suitable medium, at moderate temperatures, e.g., 10° to 100° C. preferably at 15° to 35° C. Where the hydroxy, (lower) acyloxy or (lower) alkoxy contributing agent is a liquid under the process conditions, it may be used in excess to serve as the medium.

Strong protonating agents include mineral acids, such as HCl, or sulfuric acid, and aromatic- or (lower) aliphatic sulfonic acids, such as p-toluenesulfonic acid. Suitable hydroxy, (lower) acyloxy or (lower) alkoxy anion contributing agents include lower alkanols, such as methanol, esters such as ethyl orthoformate, or organic acids or anhydrides, such as acetic acid or acetic anhydride, singly or in mixtures.

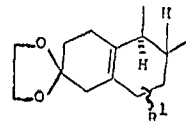
The term (lower) acyloxy is herein intended to include those groups having from 2 to 4 carbon atoms, such as acetoxy, propionyloxy and butyryloxy, preferably acetoxy; while the term (lower) alkoxy is intended to include those groups having from 1 to 4 carbon atoms, such as methoxy, ethoxy, propoxy, and butoxy, and their isomeric forms, preferably those which have straight chains.

As will be readily appreciated by those skilled in the art, in the preparation of Compounds I, various intermediates may be used having "protected" forms, as described below:

When the desired Z structure is Za where R²=H, then the group as protected may be as represented by Formula P1 or P2,



(P1)

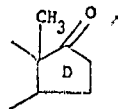


(P2)

in which R¹ has the above significance and R⁴ represents tetrahydropyran-2yl, tetrahydrofuran-2-yl or an alkyl

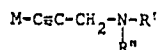
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Alternatively, Compounds IV may be prepared by reacting (Process d1) a suitable 17-keto-steroid (a Compound VIII), the D ring of which may be conveniently represented by the formula:



(VIII) 10

with a suitable organo-metallo reagent (Compound IX)



(IX) 15

wherein R' and R'' are as defined above, and M is an equivalent unit of either an active metal or a polyvalent active metal halide, e.g. an alkali metal, such as lithium, potassium or sodium, aluminum, zinc, or magnesium bromide or iodide to obtain an intermediate (Compound X) which on hydrolysis (Process d2) yields the desired Compound IV.

Process d1 may be carried out under conditions conventionally employed in carrying out "Grignard-type" reactions, e.g., in an aprotic organic medium at a temperature of from about -30°C . to 100°C ., preferably from about -20°C . to 50°C . followed by standard hydrolysis (Process d2) of the resulting M salt of the resultant Compound IV in an aqueous medium, e.g., water or a highly concentrated aqueous salt solution, e.g., saturated ammonium chloride solution. The medium used is dependent upon the composition of the organo-metallo reagent. For example, if M is MgBr, MgI or Li, the medium may be ether or tetrahydrofuran, if M is Na, the medium may be liquid ammonia-ether, liquid ammonia-tetrahydrofuran, dioxane, pyridine or dioxane-pyridine. In Process d1, the temperature and medium are not critical. Likewise, in Process d2, the temperature and hydrolyzing solution are not critical.

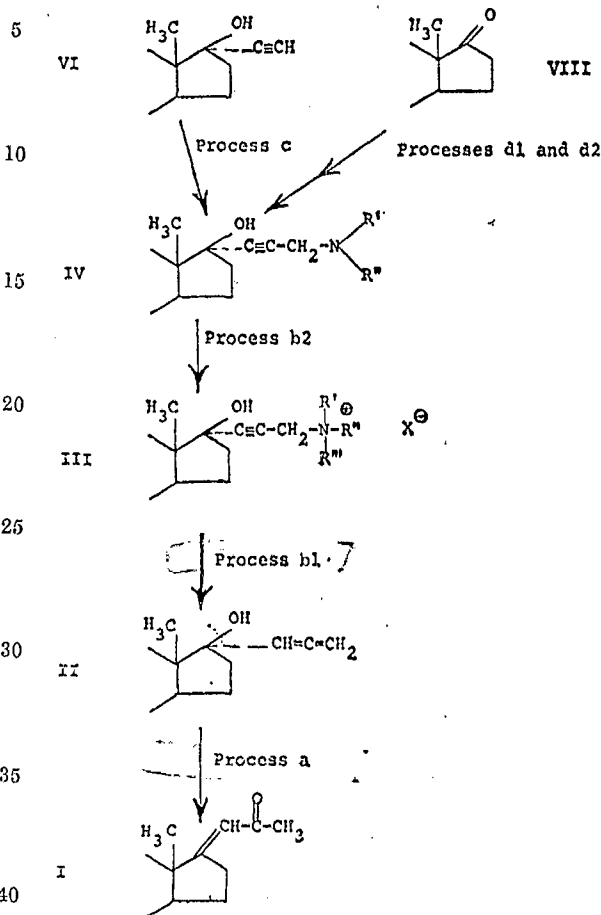
The above-described starting materials and reactants, e.g., reducing agent, Compounds V, VI, VII, VIII and IX are known and may be prepared as described in the literature, or where not known may be prepared by methods analogous to those described in the literature.

The starting material (Compound III) for the reduction step (Process b1) should be in a protected form, otherwise a 3-keto function of a Z moiety could be affected, if present. Accordingly, once Compound II is obtained, in the protected form, it may then be "deprotected" by acid treatment or alternatively, used in the protected form in Process a resulting in conversion of such protected Compound II to the corresponding "deprotected" Compound I, i.e., the reaction at the 17-position (Process a)-and "deprotection" occurring concomitantly.

Conversion of a "protected" form of compound, i.e. from its P form to its corresponding Z form, is achieved by "acid-rearrangement" under conditions conventionally employed for cleaving a 3-enol ether on a 2,5(10) unsaturated steroid or an ethylenedioxy on a saturated benzoin ring to a 3-keto-4-unsaturated steroid, i.e. (Process p). Process p may be effected under vigorous conditions, e.g., with oxalic acid or hydrochloric acid, at a pH value for example between 1 and 2, or if desired may be effected under milder conditions preferably with oxalic acid, acetic acid or generally in acid media with pH value above 2 and preferably between 3 and 5, and preferably for a period of at least about 3 hours. Either procedure may be carried out, e.g. at temperatures from 0° to 50°C ., and if desired, in the presence of suitable inert organic solvent, such as a lower alkanol, e.g., methanol, when mineral acid is employed; however, when the acid reactant is liquid it may be employed in excess to serve as solvent, e.g., acetic acid.

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The above-described processes are conveniently represented by the following reaction scheme in which only the D rings of the compounds are depicted:



The Compounds I, of this invention are useful because they possess pharmacological properties in animals. In particular, such compounds are useful as fertility control agents in animals, as they possess progestational activity as indicated by standard tests, e.g., the well known Clauberg test or the method basically described in Endocrinology, 63 (1958), 464.

These compounds may be combined with a pharmaceutically acceptable carrier or adjuvant. They may be administered orally or parenterally. The dosage will vary depending upon the mode of administration utilized and the particular compound employed. However, in general, satisfactory results are obtained when the compounds are administered at a daily dosage of from about 1 milligram to 20 milligrams. This daily dosage is preferably given in single or equally divided doses, e.g., 1 to 2 times a day, or in sustained release form. It will be appreciated by those skilled in the art, that the daily dosage level is independent of body weight. Dosage forms suitable for internal administration comprise from about 0.5 milligram to 20 milligrams of the compound in admixture with a solid or liquid pharmaceutical carrier or diluent.

The preferred pharmaceutical compositions from the standpoint of preparation and ease of administration are solid compositions, particularly hard-filled capsules and tablets containing from about 0.5 milligram to 20 milligrams of the active ingredient. Tablets may contain the active ingredient in admixture with conventional pharmaceutical excipients, e.g., inert diluents, such as calcium carbonate, sodium carbonate, lactose and talc, granulating and disintegrating agents, e.g., starch and alginic acid, binding agent, e.g., starch, gelatin and acacia, and lubricating agents, e.g., magnesium stearate, stearic acid and talc. The tablets may be uncoated or coated by known