The First Synthesized Oral Contraceptive U.S. Patent #2,744,122, Rare Original (Patented 1956)

Curated by Stephen A Batman

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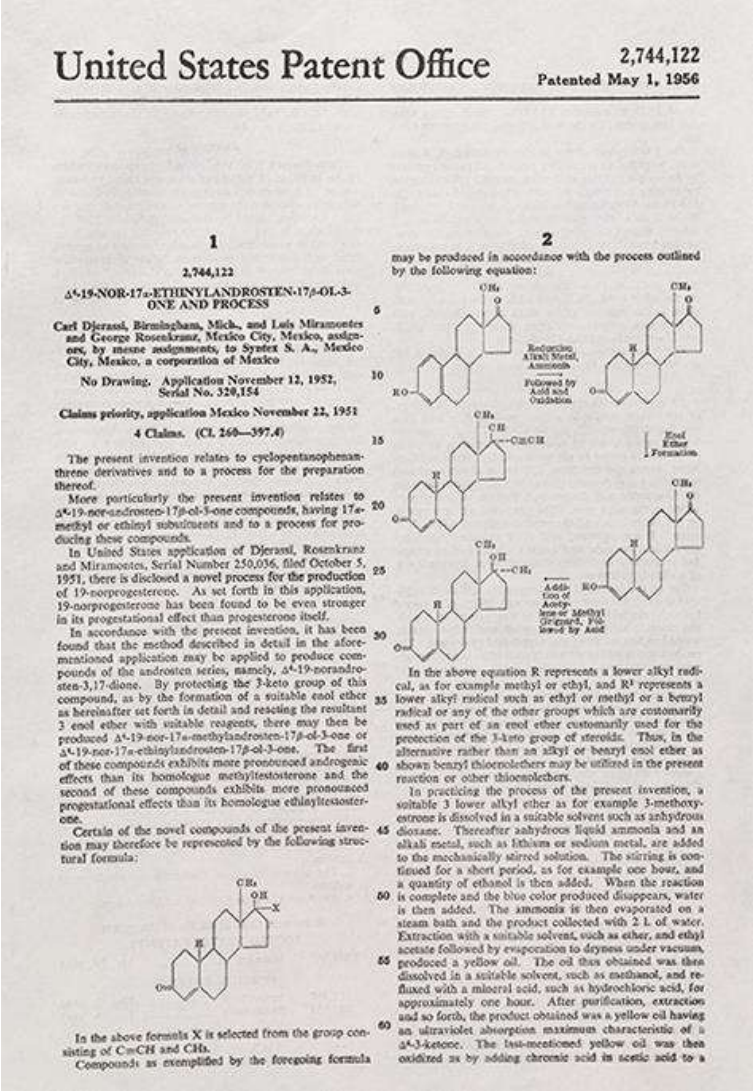
Summary of this Original U.S. Patent

Carl Djerassi, Luis Miramontes, and George Rosenkranz, Original U.S. Patent #2,744,122, May 1, 1956



United States Patent Office 2,744,122 Patented May 1, 1956

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2,744,122

Δ⁴-19-NOR-17α-ETHINYLANDROSTEN-17β-OL-3-ONE AND PROCESS

Carl Djerassi, Birmingham, Mich., and Luis Miramontes and George Rosenkranz, Mexico City, Mexico, assignors, by mesne assignments, to Syntex S. A., Mexico City, Mexico, a corporation of Mexico

No Drawing. Application November 12, 1952, Serial No. 320,154

Claims priority, application Mexico November 22, 1951

4 Claims. (Cl. 260—397.4)

The present invention relates to cyclopentanophenanthrene derivatives and to a process for the preparation thereof.

More particularly the present invention relates to Δ⁴-19-nor-androsten-17β-ol-3-one compounds, having 17α-methyl or ethinyl substituents and to a process for producing these compounds.

In United States application of Djerassi, Rosenkranz and Miramontes, Serial Number 250,036, filed October 5, 1951, there is disclosed a novel process for the production of 19-norprogesterone. As set forth in this application, 19-norprogesterone has been found to be even stronger in its progestational effect than progesterone itself.

In accordance with the present invention, it has been found that the method described in detail in the aforementioned application may be applied to produce compounds of the androsten series, namely, Δ⁴-19-norandrosten-3,17-dione. By protecting the 3-keto group of this compound, as by the formation of a suitable enol ether as hereinafter set forth in detail and reacting the resultant 3 enol ether with suitable reagents, there may then be produced Δ⁴-19-nor-17α-methylandrosten-17β-ol-3-one or Δ⁴-19-nor-17α-ethinylandrosten-17β-ol-3-one. The first of these compounds exhibits more pronounced androgenic effects than its homologue methyltestosterone and the second of these compounds exhibits more pronounced progestational effects than its homologue ethinyltestosterone.

Certain of the novel compounds of the present invention may therefore be represented by the following structural formula:

In the above formula X is selected from the group consisting of C≡CH and CH₃.

Compounds as exemplified by the foregoing formula may be produced in accordance with the process outlined by the following equation:

In the above equation R represents a lower alkyl radical, as for example methyl or ethyl, and R¹ represents a lower alkyl radical such as ethyl or methyl or a benzyl radical or any of the other groups which are customarily used as part of an enol ether customarily used for the protection of the 3-keto group of steroids. Thus, in the alternative rather than an alkyl or benzyl enol ether as shown benzyl thioenolethers may be utilized in the present reaction or other thioenolethers.

In practicing the process of the present invention, a suitable 3 lower alkyl ether as for example 3-methoxy-estrone is dissolved in a suitable solvent such as anhydrous dioxane. Thereafter anhydrous liquid ammonia and an alkali metal, such as lithium or sodium metal, are added to the mechanically stirred solution. The stirring is continued for a short period, as for example one hour, and a quantity of ethanol is then added. When the reaction is complete and the blue color produced disappears, water is then added. The ammonia is then evaporated on a steam bath and the product collected with 2 l. of water. Extraction with a suitable solvent, such as ether, and ethyl acetate followed by evaporation to dryness under vacuum, produced a yellow oil. The oil thus obtained was then dissolved in a suitable solvent, such as methanol, and refluxed with a mineral acid, such as hydrochloric acid, for approximately one hour. After purification, extraction and so forth, the product obtained was a yellow oil having an ultraviolet absorption maximum characteristic of a Δ⁴-3-ketone. The last-mentioned yellow oil was then oxidized as by adding chromic acid in acetic acid to a

stirred solution of the oil in acetic acid at a temperature below 20° C. Purification of the oxidation product produced Δ^4-19-norandrosten-3,17-dione, which was a valuable intermediate for the further steps of the present process.

The 3-keto group of the Δ^4-19-norandrosten-3,17-dione could be protected for further steps in the present process by forming a suitable enol ether thereof. For example, by treating the compound with ethyl orthoformate, the $\Delta^{3,5}$-19-nor-3-ethoxy-androstadien-17-one was formed. If the 3 enol ether thus formed is then treated with a suitable methyl Grignard reagent, such as methyl magnesium bromide in a suitable solvent, such as anhydrous ether, followed by acidification with a suitable mineral acid, such as hydrochloric acid, there is then produced a novel Δ^4-19-nor-17α-methyl-androsten-17β-ol-3-one. If, on the other hand, the 3 enol ether is treated with acetylene in the presence of an alkali metal alkoxide, such as potassium tertiary amyloxide, there is formed Δ^4-19-nor-17α-ethinylandrosten-17β-ol-3-one.

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

Example I

7.5 g. of 3-methoxyestrone were dissolved in 750 cc. of anhydrous dioxide in a three-neck flask, placed in a box and insulated with cotton wool. 2 l. of anhydrous liquid ammonia and 15 g. of lithium metal in the form of wire were added to the mechanically stirred solution. After stirring for one hour, 150 cc. of absolute ethanol were added at such speed that no bumping occurred; when the blue color had disappeared, 500 cc. of water were added in the same way. The ammonia was evaporated on the steam bath and the product collected with 2 l. of water. It was extracted with ether and then with ethyl acetate and the combined extract was washed to neutral and evaporated to dryness under vacuum, leaving 7.4 g. of a slightly yellow oil.

The oil thus obtained was dissolved in 400 cc. of methanol and refluxed during one hour with 150 cc. of 4-normal hydrochloric acid. The mixture was poured in a sodium chloride solution and extracted with ethyl acetate, washed to neutral, dried and evaporated to dryness. The product was a yellow oil which showed an ultraviolet absorption maximum at 240μ(log ϵ4.31), characteristic of a Δ^4-3-ketone.

A solution of 2.7 g. of chromic acid in 20 cc. of water and 50 cc. of acetic acid was added to the stirred solution of the above oil in 100 cc. of acetic acid, maintaining the temperature below 20° C. After 90 minutes standing, 50 cc. of methanol were added and the mixture concentrated under vacuum (20 mm.). The residue was extracted with ether, washed to neutral and evaporated to dryness. The residual semi-crystalline product (7 g.) was chromatographed over alumina and the fractions eluted with ether yielded 3.2 g. of Δ^4-19-norandrosten-3,17-dione having a melting point of 163°–167° C.

Example II

Following the method described in Example I, but using 15 g. of sodium instead of lithium, exactly the same results were obtained.

Example III

A solution of 2 g. of Δ^4-19-norandrosten-3,17-dione and 0.4 g. of pyridine hydrochloride in 50 cc. of benzene free of thiophene was made free of moisture by distilling a small portion 4 cc. of absolute alcohol and 4 cc. of ethyl orthoformate were added and the mixture was refluxed during 3 hours. 5 cc. of the mixture were then distilled and after adding an additional 4 cc. of ethyl orthoformate the refluxing was continued for two hours longer. The mixture was evaporated to dryness under vacuum and the residue was taken up in ether, washed, dried and evaporated to dryness. The residue was crystallized from

hexane-acetone and then from ether to give $\Delta^{3,5}$-19-nor-3-ethoxy-androstadien-17-one with a melting point of 140°–142° C., $[\alpha]_D$—83.05°, ultraviolet absorption maximum at 242μ(log ϵ4.4).

Example IV

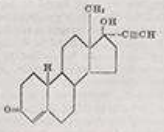
A solution of 1 g. of $\Delta^{3,5}$-19-nor-3-ethoxy-androstadien-17-one in 10 cc. of anhydrous ether was added to a solution of 10 g. of methyl magnesium bromide in 25 cc. of anhydrous ether and the mixture was refluxed during two hours and then poured in water, acidified with 50% hydrochloric acid to pH 1 and left standing for one hour. The product was extracted with ether, washed to neutral, dried and evaporated to dryness. Several crystallizations from ether-hexane yielded Δ^4-19-nor-17α-methyl-androsten-17β-ol-3-one with a melting point of 154°–156° C., $[\alpha]_D$+30.3°, ultraviolet absorption maximum at 240μ(log ϵ4.32).

Example V

1 g. of potassium metal was dissolved in 25 cc. of tertiary amyl alcohol by heating under an atmosphere of nitrogen. 1 g. of $\Delta^{3,5}$-19-nor-3-ethoxyandrostadien-17-one in 25 cc. of anhydrous toluene was added and nitrogen was passed during 15 minutes. Then acetylene (especially dried and purified) was passed during 14 hours through the mechanically stirred solution, at room temperature. The mixture was poured in water, acidified to pH 1 with dilute hydrochloric acid, heated on the steam bath for 30 minutes and then subjected to steam distillation to remove the organic solvents. The residue was filtered, dried and recrystallized several times from ethyl acetate. The Δ^4-19-nor-17α-ethinylandrosten-17β-ol-3-one thus obtained had a melting point of 198°–200° C. (in sulphuric acid bath), 200°–204° C. (Kofler), $[\alpha]_D$—31.73°, ultraviolet absorption maximum at 240μ(log ϵ4.38).

We claim:

1. A process for the production of a compound having the following formula:



which comprises reducing a lower alkyl ether of estrone with an alkali metal in liquid ammonia followed by hydrolysis with a mineral acid and oxidation with chromic acid to form Δ^4-19-norandrosten-3,17-dione, selectively forming a 3-enol ether of said dione and treating said ether with acetylene in the presence of an alkali metal alkoxide, followed by hydrolysis with a mineral acid.

2. The process of claim 1 wherein the alkali metal is lithium.

3. The process of claim 1 wherein the alkali metal is sodium.

4. Δ^4-19-nor-17α-ethinylandrosten-17β-ol-3-one.

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THE FIRST SYNTHESIZED ORAL CONTRACEPTIVE: ORIGINAL U.S. PATENT OFFICE PRINTING OF PATENT #2,744,122, FOR NORETHISTERONE, USED BY GREGORY PINCUS IN CLINICAL TRIALS AND EVENTUALLY MARKETED AS ONE OF THE FIRST BIRTH-CONTROL PILLS IN THE UNITED STATES

Rare original United States Patent Office printing of patent number 2,744,122, the patent for norethisterone, the first synthesized oral contraceptive, developed from Mexican yams by a team of chemists led by Carl Djerassi in 1951, and one of three synthesized oral contraceptives used by Gregory Pincus—with whom Djerassi shares the title of "the father of birth control pill"—in early clinical trials.

Djerassi started working at the small pharmaceutical company Syntex in Mexico City in 1949. There he established how to synthesize cortisone from a natural product derived from the Mexican yam. He then found that the same starting compound could yield norethisterone, a mimic of progesterone, which controls the female menstrual cycle. Norethisterone was the first highly active oral progestogen to be synthesized, followed soon after by noretynodrel (1952) and norethandrolone (1953), which were synthesized by Frank B. Colton at Searle in Skokie, Illinois.

In early 1951, reproductive physiologist Gregory Pincus, a leader in hormone research and co founder of the Worcester Foundation for Experimental Biology (WFEB) in Shrewsbury, Massachusetts, first met American birth control movement founder Margaret Sanger at a Manhattan dinner hosted by Abraham Stone, medical director and vice president of Planned Parenthood. Stone helped Pincus obtain a small grant to begin hormonal contraceptive research.

Unbeknownst to Pincus, Sanger and Stone, the actual chemistry of the Pill had already been invented, but neither Djerassi nor the obscure Mexico City lab where he worked had tested their orally effective form of synthetic progesterone as a contraceptive. Pincus' research started on April 25, 1951, with reproductive physiologist Min Chueh Chang continuing the 1937 experiments of Makepeace, et al. which showed that injections of progesterone suppressed ovulation in rabbits. Progesterone was abandoned as an oral ovulation inhibitor following these clinical studies due to the high and expensive doses required, incomplete inhibition of ovulation, and the frequent incidence of breakthrough bleeding.

Looking for an alternative, Pincus asked his contacts at pharmaceutical companies to send him synthetic chemical compounds with progestogenic activity. Chang screened nearly 200 chemical compounds in animals and found the three most promising were Djerassi's norethisterone [the present patent] and Colton's noretynodrel and norethandrolone.

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Ultimately Pincus and Rock selected Colton's noretynodrel for the first contraceptive trials in women, citing its total lack of androgenicity versus Djerassi's norethisterone very slight androgenicity in animal tests. When combined with mestranol, noretynodrel was given the

proprietary name Enovid, which went on to become the first oral contraceptive marketed as such in the United States in 1960.

Both Enovid and Norlutin (norethisterone) were approved in the U.S. for gynecological disorders such as endometriosis as early as 1957, and both were used off label for birth control purposes. While Enovid was the first to be marketed as a birth-control pill, norethisterone—when combined with mestranol—was named Ortho-Novum in the United States in 1963 and prescribed for birth control, making it the second progestin after Enovid to be used in an oral contraceptive.

While both Pincus and Djerassi have alternately been called "the father of the birth control pill," Djerassi was among the earliest of scientists to pioneer the chemical bases of what would become the Pill, and he would be the first to gain national recognition for his contribution.

He was inducted into the National Inventors Hall of Fame in 1978 for patent 2,744,122 (this one). Colton was inducted a decade later in 1988 for patents 2,691,028; 2,725,389. Pincus was inducted nearly three decades later in 2006 for 2,666,015.

By chemically synthesizing a steroid mimic of the hormone progesterone, Djerassi paved the way for the oral contraceptive pill, allowing women for the first time to safely and reliably take control of their own reproductive choices. Djerassi's conviction that the Pill made the sexual liberalization of the 1960s possible is widely shared, and chemical control of the fertility cycle was a key ingredient in subsequent advances in reproductive technologies, beginning with in vitro fertilization (IVF) in the late 1960s.

DJERASSI, Carl; MIRAMONTES, Luis and ROSENKRANZ, George.
United States Patent Office 2,744,122. Patented May 1, 1956. Delta4-19-NOR-17alpha ETHINYLANDROSTEN-l7beta-OL-3-ONE and Process. [Washington, DC: United States Patent Office, 1956]. Quarto (7-1/2 by 11 inches), single leaf of wove paper printed on recto and verso for two pages; custom card portfolio.

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