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17α-METHYL-19-NORTESTERONE

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4 Claims. (Cl. 260—397.4)

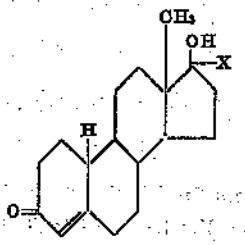
The present invention relates to cyclopentanophenanthrene derivatives and to a process for the preparation thereof.

More particularly the present invention relates to Δ^4-19-nor-androsten-17β-ol-3-one compounds, having 17α-methyl or ethynil 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.

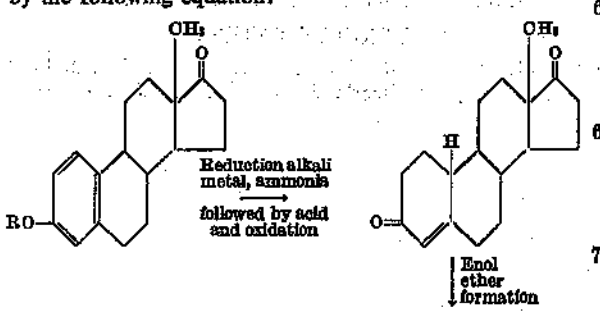
In accordance with the present invention, it has been found that the method described in detail in the aforementioned application may be applied to produce compounds of the androsten series, namely, Δ^4-19-norandrosten-3,17-dione. By protecting the 3-keto group of this compound, as by the formation of 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 Δ^4-19-nor-17α-methylandrosten-17β-ol-3-one or Δ^4-19-nor-17α-ethynilandrosten-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 ethyniltestosterone.

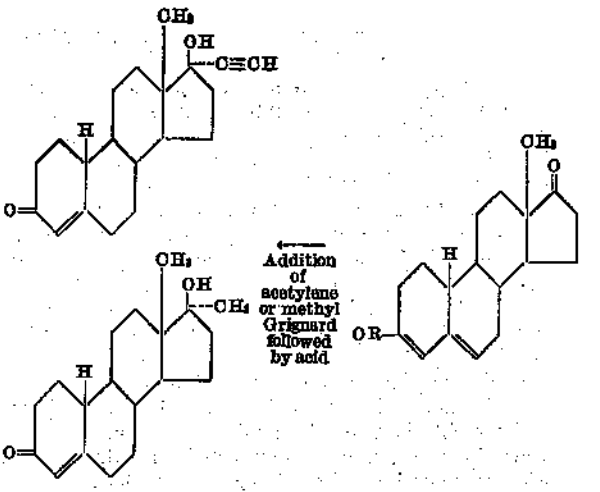
Certain of the novel compounds of the present invention may therefore be represented by the following structural formula:



In the above formula X is selected from the group consisting of C≡CH and CH_3.

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 R^1 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 production 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-esterone 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 lt. 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 Δ^4-3-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 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-ethanylandrosten-17β-ol-3-one.