6-METHYL-17α-HYDROXY-4-PREGNENE-3,20-DIONE AND PROCESSES FOR ITS PREPARATION

The present invention relates to a new steroid and to a novel process for its preparation. More particularly, this invention relates to 6-methyl-17α-hydroxy-4-pregnene-3,20-dione.

The compound of this invention can be conveniently prepared from 6-methyl-3β-hydroxy-5,16-pregnadien-20-one or its esters. An alkaline solution of the steroid is treated with a mild epoxidizing agent, such as alkaline hydrogen peroxide, to form 3β-hydroxy-6-methyl-16α,17α-epoxy-5-pregnen-20-one which upon Oppenauer oxidation yields 6α-methyl-16α,17α-epoxy-4-pregnene-3,20-dione. This compound is then transformed into 6α-methyl-16-bromo-17α-hydroxy-4-pregnen-3,20-dione by treatment with hydrobromic acid in an organic solvent such as chloroform or a lower alkanoic acid. The bromohydrin is then converted to the 6α-methyl-17α-hydroxy-4-pregnene-3,20-dione by use of a hydrogenation catalyst such as palladium or Raney nickel. Typically, palladium can be used adsorbed on calcium carbonate or on ammonium acetate. With the palladium catalysts a solution of the bromohydrin in a solvent such as ethanol is stirred at room temperature until one molecular equivalent of hydrogen has been absorbed. Another useful hydrogenation catalyst is Raney nickel; this can be used in alcoholic solution at reflux temperature.

The compound of this invention is a valuable

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intermediate for the preparation of progestationally active hormones, such as 6α-methyl-17α-acetoxy-progesterone.

This invention will appear more fully from the Examples which follow. In these Examples, temperatures are given in degrees Centigrade (°C.) and quantities of materials in parts by weight.

EXAMPLE 1

To a solution of 100 parts of 3β-acetoxy-5(6),-22α-spirosten (diosgenin acetate) in 748 parts of chloroform maintained at 0°C. are added 50 parts of monoperphthalic acid dissolved in ether. After standing at room temperature for 15 hours, the solution is filtered to remove the insoluble material and the filtrate is washed to neutrality with water. The filtrate is concentrated nearly to dryness on a steam bath and 400 parts of methanol are added. The solution is then concentrated to a volume of about 225 parts. The precipitate which forms is collected on a filter, and upon recrystallization from methanol there is obtained 3β-acetoxy-5α,6α-epoxy-22α-spirostan melting at about 231-233°C.

A solution of 40 parts of 3β-acetoxy-5α,6α-epoxy-22α-spirostan in 522 parts of benzene is cooled to 0°C., and 400 parts of a 3 molar solution of methylmagnesium bromide in ether is slowly added. The resulting solution is refluxed for 8 hours and the excess methylmagnesium bromide is then decomposed by the slow addition of water. A small amount of a 5% solution of sulfuric acid is added to dissolve any precipitate which may have formed. The organic layer is separated, washed with water to neutrality, and evaporated to dryness on a steam bath. Upon recrystallization from a solution of chloroform and methanol there is obtained 3β,5α-dihydroxy-6β-methyl-22α-spirostan melting at about 220-222°C.

A solution of 43 parts of 3β,5α-dihydroxy-6β-methyl-22α-spirostan (5α-hydroxy-6β-methyltigogenin) in 200 parts of acetic anhydride is maintained at 195°C. for 8 hours and then is diluted with 500 parts of a 90%

aqueous solution of acetic acid. The solution is cooled to about 15°C. and a solution of 17.5 parts of chromium trioxide in 40 parts of water and 200 parts of acetic acid is added. The mixture is allowed to stand at room temperature for about 30 minutes, and then is distilled under vacuum until a viscous oil is obtained. Approximately 100 parts of 80% acetic acid are added to this oil and the mixture is refluxed for 2 hours. Then water is added to the solution and the precipitate which forms is extracted with ethyl acetate. The extract is distilled to dryness. The residual yellowish green oil is taken up in ether and applied to a chromatography column containing silica gel. The column is developed with benzene and benzene solutions containing increasing amounts of ethyl acetate. Elution with a 10-15% solution of ethyl acetate in benzene affords 3β-acetoxy-6-methyl-5,16-pregnadien-20-one melting at about 114.5-117°C. Recrystallized from aqueous acetone it melts at about 121-122.5°C. The compound shows absorption in the infrared at 5.80, 6.02 and 6.31 microns.

EXAMPLE 2

To a solution of 5 parts of 3β-acetoxy-6-methyl-5,16-pregnadien-20-one in 240 parts of methanol, 1.8 parts of sodium hydroxide and 10 parts of water are added 18 parts of a 35% hydrogen peroxide solution. This mixture is allowed to stand at room temperature for 24 hours and is then poured into water. The precipitate which forms is extracted with chloroform. The chloroform solution is washed with water, dried over anhydrous sodium sulfate

and evaporated nearly to dryness. Ether is added to the residue and the precipitate which forms is collected by filtration. Upon recrystallization from a mixture of acetone and ether there is obtained 3β-hydroxy-6-methyl-16α,17α-epoxy-5-pregnen-20-one melting at about 189-190°C. The compound shows a specific rotation in chloroform of -4.17°.

EXAMPLE 3

A solution of 5 parts of 3β-hydroxy-6-methyl-16α,17α-epoxy-5-pregnen-20-one in 87 parts of toluene is distilled until 22 parts of the solvent has been removed, after which there is added 47 parts of cyclohexanone, 10 parts of aluminum isopropoxide, and 86 parts of toluene. The mixture is refluxed for 30 minutes and then cooled to room temperature. It is poured into ice water which has been acidified with a small amount of dilute sulfuric acid, and then extracted several times with benzene. The benzene extracts are combined and steam distilled to eliminate the cyclohexanone, and then extracted with ether. The ethereal solution is washed with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue is taken up in benzene and applied to a chromatography column containing alumina. The column is developed with benzene and benzene solutions containing increasing amounts of hexane. Upon elution with a 50% solution of hexane in benzene there is obtained 6α-methyl-16α,17α-epoxy-4-pregnene-3,20-dione melting at about 130-134°C. The compound

has the specific rotation of +129.5° and shows absorption in the ultraviolet at 240 millimicrons with an extinction coefficient of about 15,830.

EXAMPLE 4

A solution of 0.5 parts of 6α-methyl-16α,17α-epoxy-4-pregnene-3,20-dione in acetic acid is reacted with hydrobromic acid for 30 minutes. The mixture is poured into ice water and the bromohydrin is collected by filtration. After drying, the bromohydrin is dissolved in methanol and refluxed for 2 hours with twice its weight of Raney nickel. The catalyst is removed by filtration and the solution is evaporated nearly to dryness. The residue is allowed to stand at room temperature for 15 hours. Upon recrystallization of the colorless needles from a mixture of water and acetone there is obtained 17α-hydroxy-6α-methyl-4-pregnene-3,20-dione melting at about 215-217°C. with a specific rotation in chloroform of +78°. The compound shows absorption in the ultraviolet at 240 millimicrons with an extinction coefficient of about 15,800.

EXAMPLE 5

A solution of 10 parts of 17α-hydroxy-6α-methyl-4-pregnene-3,20-dione in 162 parts of acetic anhydride and 1.5 parts of p-toluenesulfonic acid is agitated at room temperature for 15 hours. The solution is then cooled in an ice bath and 200 parts of water are slowly added, until the excess anhydride is destroyed. The precipitate is collected on a filter and dried.

Upon recrystallization from methanol there is obtained 17α-acetoxy-6α-methyl-4-pregnen-3,20-dione melting at about 214.5 - 216°C. The compound shows absorption in the ultraviolet at 241 millimicrons with an extinction coefficient of about 16,750.