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REDUCTION OF 11-KETOPROGESTERONE TO 3β-HYDROXYALLOPREGNANE-11,20-DIONE

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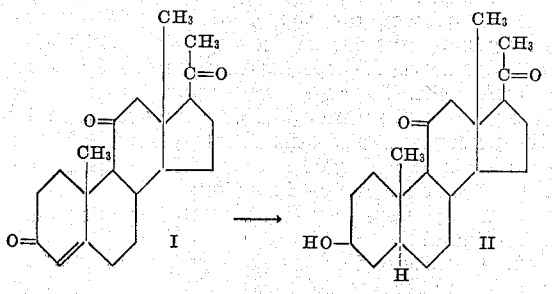
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1

The present invention relates to a process for the hydrogenation of a steroid and is more particularly concerned with a process for the hydrogenation of 11-ketoprogesterone.

The novel process may be represented by the following formulae:



wherein the hydrogenation of the 11-ketoprogesterone in the presence of a specific catalyst, a platinum catalyst, proceeds in one step to 3β-hydroxyallopregnane-11,20-dione.

While hydrogenation of steroid compounds containing double bonds as well as keto groups have frequently been carried out, there is no reference in the art showing any method for the reduction of a 3-keto-Δ^4-grouping in almost quantitative yield and in one step to a 3β-ol-saturated steroid or allosteroid. Reduction of double bonds of steroid compounds without simultaneous reduction of keto groups is known, a recent example being the hydrogenation of 11α-hydroxyprogesterone to give 11α-hydroxypregnane-3,20-dione and 11α-hydroxyallopregnane-3,20-dione. Similarly, the reduction with hydrogen of a 3-keto group to a 3-carbinol group in a steroid without concomitant reduction of double bonds is known. For example, Ruzicka [U. S. Patent 2,168,685] shows reduction of 3-keto-Δ^5-steroids to 3α-ol-Δ^5-steroids by catalytic hydrogenation. In other hydrogenations of steroids, mixtures of compounds were obtained. For example, W. H. Perlman, J. Biol. Chem. 166, pp. 473–476 (1946) hydrogenated progesterone, obtaining a mixture of compounds apparently containing both the corresponding normal and allo steroid compounds. In order to obtain pure compounds instead of mixtures, reduction of steroids possessing both keto groups and double bonds was carried out in two steps. For example, cholestenone, a compound possessing a 3-keto-Δ^4-grouping, was hydrogenated to the saturated compound coprostanone in the presence of a palladium catalyst, and was then hydrogenated to coprostanol with a platinum catalyst in acidic solution (summarized in Fieser and Fieser, Natural Products Related to Phenanthrene, 3rd edition, Reinhold Publishing Corporation, New York, N. Y., 1949, page 99). In view of this art, it is considered an entirely unexpected and unpredictable result, that 11-ketoprogesterone can be hydrogenated to 3β-hydroxyallopregnane-11,20-dione in nearly quantitative yields and in a single step.

2

An object of the present invention is to provide a novel process for the hydrogenation of 11-ketoprogesterone in such a manner that the 3-keto-Δ^4-grouping thereof is reduced and hydrogenated in one step and the corresponding 3-hydroxyallosteroid is obtained. A further object of this invention is to provide a process wherein the above-cited hydrogenation takes place without concomitant reduction of keto groups in positions 11 and 20. Other objects of the invention will be apparent to one skilled in the art to which this invention pertains.

The utility of this process resides in the fact that 11-ketoprogesterone (I) can be hydrogenated in very high yield in one step to 3β-hydroxyallopregnane-11,20-dione (II) rather than in two steps. This latter compound may then be converted to cortisone acetate by a process shown by Kritchevsky et al., J. Am. Chem. Soc. 74, 483 (1952) in conjunction with a process by Djerassi, Nature, 168, 28 (1951). If in Kritchevsky's process 3β-hydroxyallopregnane-11,20-dione is substituted for the 3α-hydroxypregnane-11,20-dione, 17α-hydroxy-21-acetoxyallopregnane-3,11,20-trione will be obtained instead of the 17α-hydroxy-21-acetoxypregnane-3,11,20-trione. This compound, which is known in the art, has been converted by bromination, treatment with sodium iodide in acetone and dehydrohalogenation to cortisone acetate by Djerassi et al., Nature, 168, 28 (1951).

The steps necessary to obtain cortisone acetate from 3-hydroxyallopregnane-11,20-dione include: treating 3-hydroxyallopregnane-11,20-dione with acetic anhydride to obtain 3β,11,20-triacetoxy-9(11),17(20)-allopregnadiene which, by treatment with perbenzoic acid, yields 3β,11,20-triacetoxy-17(20)-oxido-9(11)-allopregnene. Hydrolysis of this compound gives 3β,17α-dihydroxyallopregnane-11,20-dione which by bromination yields 3β,17α-dihydroxy-21-bromoallopregnane-11,20-dione. Treatment of the 21-bromo compound with potassium acetate gives the corresponding 3β,17α-dihydroxy-21-acetoxypregnane-11,20-dione and oxidation furnishes the 17α-hydroxy-21-acetoxyallopregnane-3,11,20-

trione. Bromination of this compound by Djerassi's method results in 2,4-dibromo-17α hydroxy - 21 - acetoxyallopregnane - 3,11,20-trione, and this compound, when treated with sodium iodide in acetone, gives the 2-iodo-4-bromo-21-acetoxyallopregnane-3,11,20-trione which by simultaneous dehalogenation and dehydrohalogenation with collidine is converted to cortisone acetate. Neither the dibromo nor the iodobromo steroid need be isolated in the process. It is obvious that other utility accrues to the process of the invention as various other uses may be made of the 3β-hydroxyallopregnane-11,20-dione thereby produced in exceedingly high yield in but a single step operation.

In carrying out the process of the present invention, 11-ketoprogesterone, dissolved in a convenient organic solvent, e. g., methanol, ethanol, dioxane, ethyl acetate or other like solvent, with methanol being preferred, is admixed with a platinum catalyst suitably comprising finely subdivided platinum. The catalyst may be on an inert carrier, for example, kieselguhr or pumice, alone or associated with a promoter. Reduced platinum dioxide, prereduced by prior reduction of platinum dioxide with hydrogen, or by the reduction of platinum dioxide in situ during the hydrogenation and reduction of 11-ketoprogesterone may be utilized. In the preferred embodiment of the invention the catalyst is prereduced platinum dioxide. The mixture is then shaken with hydrogen in a Paar hydrogenator until two moles of hydrogen are absorbed per mole of 11-ketoprogesterone. The hydrogen pressure is maintained between about two and seventy pounds per square inch, preferably between about five and 25 pounds per square inch. The time required for the absorption may range from one half hour to forty-eight hours. After the termination of absorption, the catalyst is removed by filtration and the solvent evaporated. The 3β-hydroxyallopregnane - 3,11,20 - trione thus-obtained may be recrystallized from solvents, such as ethyl acetate, hexanes mixed with ethyl acetate, and other like solvents, or used in the crude form for further steps of synthesis.

The following example is given to illustrate the method of the present invention and is not to be construed as limiting.

Example.—Hydrogenation of 11-ketoprogesterone

Five hundred milligrams (500 milligrams) of 11-ketoprogesterone were dissolved in one hundred milliliters of C. P. methanol and 300 milligrams of prereduced platinum dioxide (PtO_2) added thereto. The mixture was introduced into a Paar hydrogenator and shaken at room temperature under about ten pounds per square inch hydrogen pressure for two hours, during which time two moles of hydrogen were absorbed. The catalyst was then removed by filtration of the suspension and the solvent was evaporated. Four hundred and ninety milligrams (490 milligrams) of material equal to a yield of about 97 percent were obtained. The material was recrystallized from ethyl acetate and exhibited a melting point of 187–188 degrees centigrade. Infrared analysis and papergram analysis of this material showed it to be pure 3β-hydroxyallopregnane-11,20-dione. Chromic acid oxidation of this material gave a quantitative yield of known allopregnane-3,11,20-trione.

In a manner similar to the example, 11-ketoprogesterone was hydrogenated in ethanol, ethyl acetate, and dioxane solutions at room temperature in the presence of prereduced platinum dioxide to give 3β-hydroxyallopregnane-11,20-dione in substantially quantitative yield.

It is to be understood that the invention is not to be limited to the exact details shown and described in the example as obvious modifications and equivalents will be apparent to one skilled in the art and the invention is therefore to be limited only by the scope of the appended claims.

We claim:

1. A process for the production of 3β-hydroxyallopregnane-11,20-dione which comprises: hydrogenating 11-ketoprogesterone in an organic solvent with hydrogen at a pressure between about two and seventy pounds per square inch, in the presence of a platinum catalyst, until about two moles of hydrogen is absorbed, to obtain 3β-hydroxyallopregnane-11,20-dione.

2. The process of claim 1 wherein the solvent is methanol.

3. A process for the production of 3β-hydroxyallopregnane-11,20-dione which comprises: hydrogenating 11-ketoprogesterone in an organic solvent with hydrogen at a pressure between about two and seventy pounds per square inch in the presence of a reduced platinum dioxide catalyst, until about two moles of hydrogen is absorbed, to obtain 3β-hydroxyallopregnane-11,20-dione.

4. A process for the production of 3β-hydroxyallopregnane-11,20-dione which comprises: hydrogenating 11-ketoprogesterone in an organic solvent with hydrogen at a pressure between about five and 25 pounds per square inch in the presence of a platinum catalyst prepared by prior reduction of platinum dioxide with hydrogen, until about two moles of hydrogen are absorbed, to obtain 3β-hydroxyallopregnane-11,20-dione.

5. The process of claim 4 wherein the solvent is methanol.

No references cited.