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PROCESS FOR THE PREPARATION OF $\Delta^{1,3,5(10)}$-3,17-DIHYDROXY STEROIDS

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4 Claims. (Cl. 260—397.4)

ABSTRACT OF THE DISCLOSURE

$\Delta^{1,3,5(10)}$-3,17-dihydroxy steroids are prepared by treatment of a $\Delta^{1,4}$-3-keto-10-methyl-17β-hydroxy steroid with an alkali metal in presence of a polycyclic aromatic compound and an ethereal solvent, followed by acid conversion of the alkali metal salt of the corresponding steroid, including the step of converting the 17β-hydroxy group to a mixed acetal and ketal. The process enables the preparation of $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene having an ether structure at the 17-position.

The invention relates to an improved process for the preparation of $\Delta^{1,3,5(10)}$-3-hydroxy-steroids by treatment of a $\Delta^{1,4}$-3-keto-10-methyl-steroid with an alkali metal in the presence of a polycyclic aromatic compound and an ethereal solvent, followed by acid conversion of the alkali metal salt of the relative steroid.

It is known that in ring A aromatic steroids can be obtained if a $\Delta^{1,4}$-3-keto-10-methyl-steroid is reacted with an anionic radical from a mixture of an alkali metal and a polycyclic aromatic compound in an ethereal solution. (e.g. British Patent 1,001,211 and corresponding patents.)

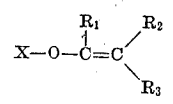
According to the above patents the starting products may possess all kinds of substituents elsewhere in the molecule, for example a 17-keto group, preferably ketalised, or a 17β-hydroxyl group, possibly converted into the tetrahydropyranyl-ether.

It has been found, however, that the yield of this process is greatly influenced by the nature of these substituents. Starting, for instance, from the $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene, a mixture is obtained from which the desired oestradiol is hard to isolate, its yield being moreover relatively low (about 15%).

Starting from a 17-ester of the $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene, there is also obtained only about 15% oestradiol.

Higher yields are obtained if the relative 17β-hydroxy-steroid is first converted into the tetrahydropyranyl-ether. But then, too, the yield of oestradiol calculated on the $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene amounts only to about 45%.

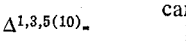
It has been found now that the yield of the present process applied to the aromatisation of $\Delta^{1,4}$-3-keto-10-methyl-17β-hydroxy-steroids is considerably increased if the 17β-hydroxy-steroid is converted into a mixed acetal or ketal obtained by the addition of the 17β-hydroxy-steroid to a vinyl-ether of the formula:



in which X=an alkyl group with 1–6 carbon atoms, and

R_1, R_2 and R_3=hydrogen or an alkyl group with 1–6 carbon atoms.

Preferably a vinyl-ether is applied of the formula:



in which Y=an alkyl group with 1–4 carbon atoms.

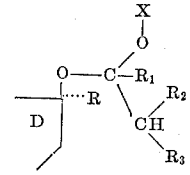
Starting, for example, from the $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene, the desired oestradiol is obtained in a yield of at least 80% calculated on the free $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene after conversion of this compound into the acetal or ketal described before.

Besides this most important and surprising increased yield, the present process has a few more advantages over the known process. Firstly the vinylalkyl-ethers to be used in the formation of the acetal or ketal are much cheaper than the dihydropyran to be used in the preparation of tetrahydropyranyl-ethers. Secondly the 17β-hydroxyl acetals or ketals derived from the above-mentioned vinylalkyl-ethers are generally obtained in a higher yield than the tetrahydropyranyl-ethers; and thirdly the final products can be isolated more easily in a pure condition than those obtained if tetrahydropyranyl-ethers are applied.

The prepara ion of the 17β-hydroxy derivatives according to the invention takes place by reacting the relative 17-hydroxy-steroid with a vinylalkyl-ether in the presence of an acid catalyst, such as paratoluene sulphonic acid, benzene sulphonic acid, dinitro benzene sulphonic acid, hydrochloric acid or a Lewis acid, such as borotrifluoride or the etherate thereof.

The reaction may be performed in the presence of a solvent, such as an aromatic hydrocarbon, for instance benzene or toluene, an ether, a halogenated hydrocarbon, such as chloroform or carbon tetrachloride, or petroleum-ether. If desired, an inhibitor, such as hydroquinone, may be added to avoid polymerisation of the vinyl-ether.

The present process also relates to the new derivatives of a $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene compound, of which the structure at carbon atom 17 is given below:



in which X, R_1, R_2 and R_3 have the meaning indicated above, and R=hydrogen or an alkyl group.

The 17-derivatives of $\Delta^{1,4}$-3-keto-10-methyl-17β-hydroxy-steroids to be used as starting products in the present process may possess yet other substituents elsewhere in the molecule and/or double bonds insofar as these groups are not sensitive to the present reductive aromatisation.

An important group of starting products are the 17-derivatives of the $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene, or the 17-alkyl derivatives thereof, which compounds lead to the valuable oestradiol, or the 17-alkyl derivatives thereof.

The aromatisation of the starting products of the present invention takes place by the known method, consisting in the reaction of such a starting product with at least two atomic equivalents of an alkali metal, and a polycyclic aromatic compound capable of serving as a radical anion precursor, e.g. biphenyl, naphthalene, methylnaphthalene, phenanthrene or anthracene, in the presence of

an ethereal solvent, followed by acidification of the resulting steroidal alkali metal salt, as more fully described in the above cited British patent.

The invention is further illustrated by the following examples:

EXAMPLE I

Thirty grams of $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene are suspended in 300 ml. of ethylvinyl-ether, after which slowly, in small portions, 100 mg. of p-toluene sulphonic acid are added. While the substance dissolves the temperature rises to about 25° C. After that the solution is stirred for 10 minutes. Next the reaction mixture is washed with 50 ml. of a 10% potassium carbonate solution, after that with water until neutral and finally evaporated to dryness.

2.9 gm. of lithium, 17.5 gm. of diphenylmethane and 37.02 gm. of phenanthrene are dissolved in 210 ml. of tetrahydrofuran in nitrogen atmosphere. The reaction mixture is refluxed and after the appearance of a bluish-green colour a solution of the above-mentioned residue in 150 ml. of tetrahydrofuran is added slowly in such a manner that the bluish-green colour is maintained. After that the mixture is stirred for 15 minutes, cooled down to 10° C., after which the lithium compounds are decomposed by the subsequent addition of 24 ml. of methanol, 10 ml. of water and 45 ml. of concentrated hydrochloric acid. After that the mixture is refluxed for 10 minutes to split off the 17-acetal group. Next the mixture is cooled down, the water layer separated and the organic layer washed with water until neutral.

The aqueous mixtures are extracted with 50 ml. of benzene and the total organic layer evaporated to dryness. The residue is boiled twice with 300 ml. of hexane and after cooling down to room temperature filtered off. The residue is dissolved in 500 ml. of boiling benzene, filtered over hyflo, and crystallised. The mother liquor is chromatographed over silicagel in benzene. The oestradiol is eluated with benzene-ethylacetate (9:1). Total yield of pure oestradiol 82% by weight=86.3% of the theory, calculated on input $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene.

From the mother liquors and the residue a small quantity of oestradiol may yet be obtained raising the conversion percentage to 87% by weight=91.5% of the theory.

Comparative examples starting from other 17-derivatives

(a) Ten grams of androstadienolone are dissolved in 250 ml. of benzene to which 20 ml. of dihydropyran are added. At normal pressure 50 ml. of benzene are distilled off. After cooling down to room temperature 1 gm. of p-toluene sulphonic acid is added, after which the mixture is stirred at room temperature for 4 hours. Next the benzene solution is extracted with a 5% potassium-carbonate solution and next washed with water until neutral. Next the benzene solution is evaporated to dryness in vacuo. The residue obtained from it is further treated as described in the previous Example I. From the resulting reaction product no crystalline matter could be obtained. By chromatography 46% by weight=48.5% of the theory of oestradiol are obtained.

(b) If the pyranyl-ether is prepared as described in Example (a), but first purified, before the reductive aromatisation takes place, 45.5% by weight=48% of the theory of oestradiol are obtained calculated on the charged quantity of androstadienolone.

(c) If in the present conversion the free androstadienolone or a 17-ester thereof is taken as starting material, the following yields are obtained:

(1) Androstadienolone: 15% by weight of oestradiol= 17% of the theory.

(2) Androstadienolone-17-hexahydrobenzoate: 15% by weight of oestradiol.

(3) Androstadienol-17-acetate: 15.4% by weight of oestradiol=16.4% of the theory.

EXAMPLE II

Starting from $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene, which compound, by the process described in Example I, has been converted into the 17-acetal, derived from methylvinyl-ether or butylvinyl-ether, after which these compounds have been aromatised reductively in accordance with Example I, pure oestradiol is obtained in a yield of 86 or 83% of the theory.

From mother liquors and residues small quantities of oestradiol can yet be recovered.

EXAMPLE III

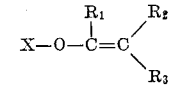
By the process described in Example I the $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene has been converted into the 17-acetal, derived from ethylvinyl-ether. Next this compound has been converted in accordance with Example I into oestradiol in a yield of 81% of the theory calculated on androstadienolone, in which the phenanthrene has been replaced by an equivalent quantity of biphenyl, however.

EXAMPLE IV

Five grams of $\Delta^{1,4}$-3-keto-17β-hydroxy-17α-methyl-androstadiene are dissolved in 50 ml. of ethylvinyl-ether, after which 25 mg. of p-toluene sulphonic acid are added. After slightly heating the mixture is maintained at room temperature for 45 minutes, after which 10 mg. of p-toluene sulphonic acid are added. If no noticeable reaction occurs, a bicarbonate solution is added, the mixture extracted with ether, washed and evaporated to dryness. The thus obtained crude $\Delta^{1,4}$-3-keto-17β-ethoxy - [1'-ethoxy]-17α-methyl-androstadiene is next treated further as described in Example I to obtain pure 17α-methyl-oestradiol in a yield of 80% of the theory.

What is claimed is:

1. In a process for the manufacture of $\Delta^{1,3,5(10)}$-3, 17-dihydroxy steroids by treatment of a $\Delta^{1,4}$-3-keto-10-methyl-17β-hydroxy steroid with an alkali metal in the presence of a polycyclic aromatic compound and an ethereal solvent, followed by acid conversion of the alkali metal salt of the corresponding steroid, the improvement which comprises converting the 17β-hydroxyl group of a $\Delta^{1,4}$-3-keto-10-methyl-17β-hydroxy-steroid into a derivative selected from the group consisting of a mixed acetal and ketal, by the addition to the 17β-hydroxy-steroid of a vinyl ether of the formula:



in which X is alkyl with 1–6 carbon atoms, and R_1, R_2, and R_3 are selected from the group consisting of hydrogen and alkyl with 1–6 carbon atoms, and employing the resulting derivative as the starting material in said process.

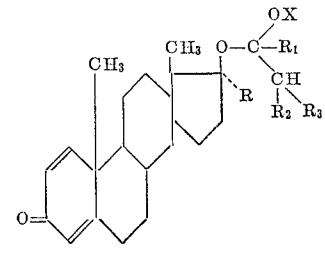
2. Process according to claim 1, in which there is employed for the formation of the derivative of the 17β-hydroxy-steroid a compound of the formula:

$$Y—O—CH=CH_2$$

in which Y is alkyl with 1–4 carbon atoms.

3. Process according to claim 1 in which the corresponding derivative of $\Delta^{1,4}$-3-keto-17β-hydroxy-androstadiene is taken as the starting material.

4. A steroid of the formula:



wherein X is alkyl with 1–6 carbon atoms, R is selected from the group consisting of hydrogen and lower alkyl, and R_1, R_2 and R_3 are selected from the group consisting of hydrogen and lower alkyl.

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