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## PROCESS FOR THE MANUFACTURE OF ALCOHOLS OF STEROIDS DOUBLY UNSATURATED IN RING A

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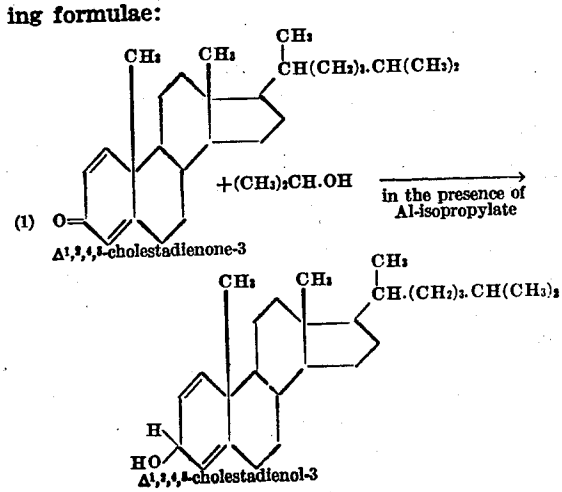
This invention relates to a process for the manufacture of alcohols of steroids doubly unsaturated in ring A.

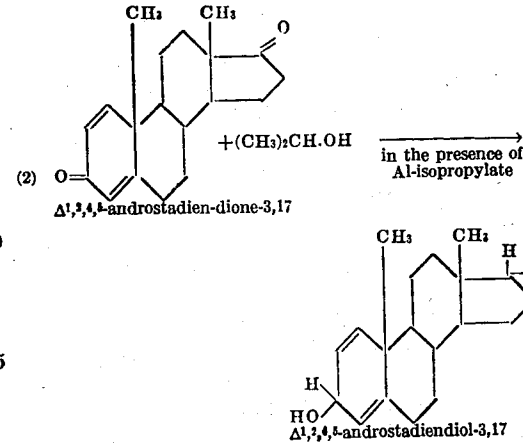
In U. S. specification Ser. No. 145,052, filed May 27, 1937, processes are described for the manufacture of unsaturated oxo-compounds of the cyclopentano-polyhydrophenanthrene series, according to which it is possible to produce 3-ketones of this class of substances containing in ring A two double bonds.

In accordance with the present invention it is possible to manufacture from these 3-ketones of steroids unsaturated in ring A, the corresponding 3-hydroxy compounds unsaturated in ring A when the reduction of the keto-group is carried out under conditions such that a hydrogenation of the double bond essentially does not occur. More especially suitable for this purpose is the use of an organic reducing medium, such as the process of interchange of oxidation stages between secondary alcohols, for example isopropyl alcohol, and oxo-compounds in the presence of metal alcoholates, for example the aluminates of the secondary alcohols used, which process has become known in principle by the work of Meerwein and R. Schmidt "Annalen der Chemie," vol. 444, page 221, and of Ponndorf "Zeitschrift für angewandte Chemie," vol. 39, page 138; further also the process of Luttringhaus described in German Patent No. 384,351.

The 3-alcohols obtained can be used either themselves as physiologically active substances or as starting materials for the production of other physiologically active substances.

The reaction may be illustrated by the following formulae:




It is indeed already known that 7-oxocholesteryl acetate and cholestenone are converted into the corresponding hydroxy-compounds with retention of the double bonds by means of isopropyl alcohol and aluminium isopropylate. From the behaviour of these singly unsaturated compounds it was not possible however to draw any conclusion as to the behaviour of such substances as contain two double bonds in ring A.

It is possible in order to raise the reaction temperature to bring about the interchange of oxidation stages also in the presence of high-boiling solvents, such as xylene and the like. In the place of aluminium alcoholates, for instance magnesium alcoholates can be used. Primary alcohols may also be used in place of secondary alcohols.

The production of the so-called 3-alcohols of the steroids from the corresponding 3-ketones is possible not only by chemical means, but may also be brought about very smoothly and in a simple manner by the use of enzymatic or phytochemical reduction methods, such as are summarised in Oppenheimer, Methoden der Fermente 1929, p. 1212, by Neuberg and Gorr.

From the work of Mamoli and Varcellone (Zeitschrift für physiologische Chemie, p. 93–5, 1937, and Berichte 70, p. 470–71, 1937) the use of fermenting yeast is indeed already known for the hydrogenation of dehydroandrosterone and androstendione compounds which are in contrast to the starting materials for the present process singly unsaturated ketones, in which the reduction takes place in the 17- and not in the 3-position. It was not possible to foresee that the reduction of the keto-group in the case of the

ketones doubly unsaturated in ring A would take place as well on the C-atom 3.

It was therefore surprising, that the enzymatic reduction of the doubly unsaturated steroid-ketones to the alcohols doubly unsaturated in ring A can be carried out under simple conditions with very good yield.

Besides those specified, also other substances of the cyclopentano-polyhydrophenanthrene series find application in the conversions set forth above, provided that they contain a keto-group in the 3-position and also in ring A two double bonds, for instance other sterol ketones, ketones of the pregnane and androstane series, bile acids, cardiac poisons, saponines and so on, as can be prepared for instance in accordance with the specification above mentioned. In the case of the compounds of the pregnane series the corresponding pregnadienols-3 will be obtained, just as in the case of the androstane compounds the corresponding androstadienols-3, one of which is illustrated above, are produced.

The alcohols of the cyclopentano-polyhydrophenanthrene series doubly unsaturated in ring A can, by a well carried out reduction, be obtained in such a degree of purity that their complete purification is possible by a single recrystallisation; if necessary, however, chemical methods of purification can be employed, the unconverted ketone being removed by condensation with ketone reagents such as semi-carbazids and the like, or the alcohol removed by the use of hydroxyl reagents. The starting material which has not entered into reaction can be again subjected to the same reduction treatment whereby an almost quantitative yield of alcohol results.

The following examples illustrate the invention:

*Example 1*

A solution of 5 g. of $\Delta^{1,2,4,5}$-cholestadienone-3 in 200 ccs. of dry isopropyl alcohol is heated to boiling with the addition of 5 g. of distilled aluminium isopropylate for 5 hours, whereby the acetone formed gradually distils off. When the reaction is complete the product is treated with ether and the reaction solution washed with dilute acid and then with water. After drying, the ether and isopropyl alcohol are evaporated. $\Delta^{1,2,4,5}$-cholestadienol-3 can be isolated from the oily residue.

*Example 2*

By treating 4 g. of $\Delta^{1,2,4,5}$-androstadiendione-3,17 in place of the corresponding cholestane compound, $\Delta^{1,2,4,5}$-androstadiendiol-3,17 is obtained in an analogous manner to Example 1.

*Example 3*

100 g. of invert sugar, 600 ccs. of water and 50 g. of yeast are mixed together. Into the actively fermenting mixture 330 mg. of $\Delta^{1,2,4,5}$-androstadien-dione-3,17 dissolved in 40 ccs. of alcohol are gradually dropped with shaking. When all has been added, the mixture is allowed to ferment further at ordinary temperature (18°–20° C.) for about 40–45 hours and then a further 20 g. of invert sugar, 200 ccs. of water and 20 g. of yeast added. After about 90 hours the fermentation is complete which can be ascertained by the only weak reducing power of the solution for Fehling's solution; the liquid is then poured off the yeast and both extracted several times with ether. The collected ethereal solutions are evaporated, the residue purified by recrystallisation from alcohol, if desired after distillation in a high vacuum, and the $\Delta^{1,2,4,5}$-androstadien-diol-3,17 thus obtained. In the same way also $\Delta^{1,2,4,5}$-cholestadienone-3 can be reduced to the corresponding $\Delta^{1,2,4,5}$-cholestadienol-3.

Of course, many other changes and variations may be made by those skilled in the art in accordance with the principles set forth herein and in the claims annexed hereto.

What we claim is:

1. Process for the manufacture of alcohols of steroids doubly unsaturated in ring A, comprising subjecting a 3-keto-steroid doubly unsaturated in ring A to the action of an agent capable of converting the keto group to a secondary alcohol group without saturation of the nuclear double bonds and selected from the class consisting of enzymatic reducing agents and a metal alcoholate employed together with an alcohol.

2. Process for the manufacture of alcohols doubly unsaturated in ring A, wherein a 3-keto-steroid doubly unsaturated in ring A is subjected to the action of an excess of an alcohol in the presence of a magnesium alcoholate until the keto group has been converted into a secondary alcohol group while the double bonds remain unreduced.

3. Process for the manufacture of alcohols of steroids doubly unsaturated in ring A, wherein a 3-keto-steroid doubly unsaturated in ring A is subjected to the action of an excess of an alcohol in the presence of a secondary alcoholate of a metal of the group consisting of aluminum and magnesium until the keto group has been converted into a secondary alcohol group while the double bonds remain unreduced.

4. Process for the manufacture of alcohols of steroids doubly unsaturated in ring A, wherein a 3-keto-steroid doubly unsaturated in ring A is subjected to an interchange of oxidation stages with a secondary alcohol in the presence of a metal alcoholate until the keto group has been converted into a secondary alcohol group while the double bonds remain unreduced.

5. Process for the manufacture of alcohols of steroids doubly unsaturated in ring A, wherein a 3-keto-steroid doubly unsaturated in ring A is reduced with an excess of an alcohol in the presence of an alcoholate of a metal of the group consisting of aluminum and magnesium.

6. Process for the manufacture of alcohols of steroids doubly unsaturated in ring A, wherein a 3-keto-steroid doubly unsaturated in ring A is subjected to an interchange of oxidation stages with an alcohol in the presence of an aluminum alcoholate.

7. Process for the manufacture of alcohols of steroids doubly unsaturated in ring A, wherein a 3-keto-steroid doubly unsaturated in ring A is subjected to the action of isopropyl alcohol and aluminum isopropylate until the keto group has been converted into a secondary alcohol group while the double bonds remain unreduced.

8. Process for the manufacture of alcohols doubly unsaturated in ring A, wherein a 3-keto-steroid doubly unsaturated in ring A is subjected to the action of an enzymatic reducing agent until the keto group has been converted into a secondary alcohol group while the double bonds remain unreduced.

9. Process as claimed in claim 8, in which the initial ketone is reduced with the aid of yeast.

10. Process for the manufacture of alcohols of steroids doubly unsaturated in ring A, wherein a

$\Delta^{1,2,4,5}$-cholestadienone-3 is subjected to an interchange of oxidation stages with a secondary alcohol in the presence of a metal alcoholate until the keto group has been converted into a secondary alcohol group while the double bonds remain unreduced.

11. Process for the manufacture of alcohols of steroids doubly unsaturated in ring A, wherein a $\Delta^{1,2,4,5}$-androstadienone-3 is subjected to an interchange of oxidation stages with a secondary alcohol in the presence of a metal alcoholate until the keto group has been converted into a secondary alcohol group while the double bonds remain unreduced.

12. Process for the manufacture of alcohols of steroids doubly unsaturated in ring A, wherein a $\Delta^{1,2,4,5}$-androstadiene-dione-3,17 is subjected to an interchange of oxidation stages with a secondary alcohol in the presence of a metal alcoholate until the keto group has been converted into a secondary alcohol group while the double bonds remain unreduced.

13. Steroid compounds that are doubly unsaturated in ring A and have one alcoholic group in 3-position.

14. A 10,13-dimethyl-cyclopentano-polyhydrophenanthrene compound doubly unsaturated in ring A and having a secondary alcoholic group in the 3-position.

15. $\Delta^{1,2,4,5}$-cholestadienol-3.

16. $\Delta^{1,2,4,5}$-androstadiendiol-3,17.

17. An androstadienol-3 having the two double bonds in ring A.

18. A pregnadienol-3 having the two double bonds in ring A.

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