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ALKALINE CLEAVAGE OF PSEUDOSAPOGENIN OXIDATION PRODUCTS

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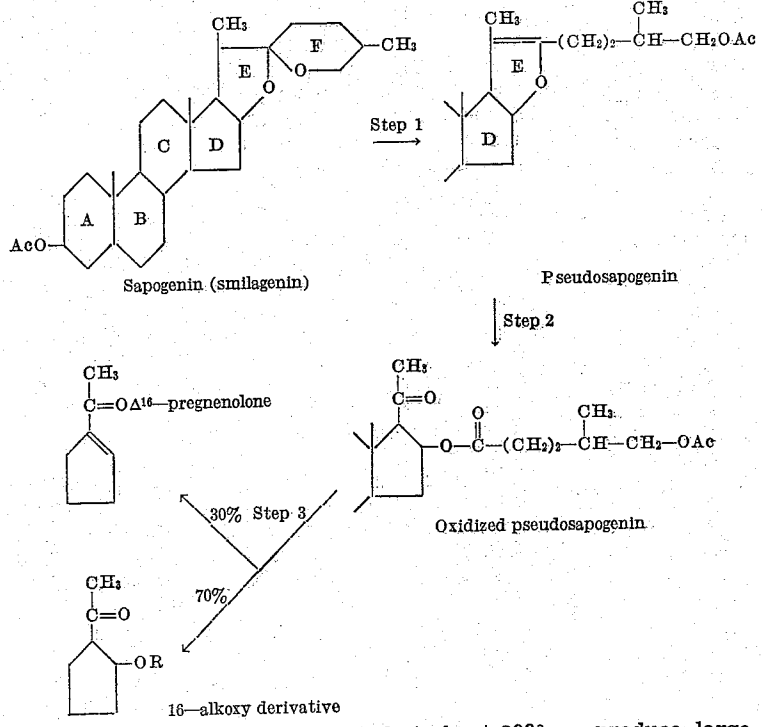
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A non-exclusive, irrevocable, royalty-free license in the invention herein described, for all governmental purposes, throughout the world, with the power to grant sublicenses for such purposes, is hereby granted to the Government of the United States of America.

This invention is related to the conversion of sapogenins to Δ^{16}-pregnenolones.

An object of this invention is to provide an improved process for making Δ^{16}-pregnenolones from sapogenins.

One of the facts that makes steroidal sapogenins useful for the production of cortisone and sex hormones is that they are convertible to Δ^{16}-pregnenolones. This conversion is conventionally carried out in three steps as is illustrated below with smilagenin, a typical steroidal sapogenin. Other steroidal sapogenins react in the same way to yield analogous Δ^{16}-pregnenolones.



In step 1 the sapogenin is heated at about 200° C. with acetic anhydride to open ring F. In step 2 the resulting pseudosapogenin is oxidized with chromium trioxide to open ring E. Then, in step 3, the conventional procedure is to cleave the ester linkages in the oxidized pseudosapogenin

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by the action of either acid or alkali in a methanolic or ethanolic solution. As indicated, the yield in this step is very poor, usually about 30%, because of the formation of large amounts of the undesirable 16-methoxy- or 16-ethoxy derivatives by reaction of the desired Δ^{16}-pregnenolone with the methanol or ethanol used as a solvent and reaction medium in this step. It is with this third step that the present invention is concerned.

In step 3 the cleavage is best accomplished in a homogeneous solution containing the alkali and the oxidized pseudosapogenin. The solvent used should readily dissolve the alkali and oxidized pseudosapogenin and should be inert to them and the final product. Methanol and ethanol, the preferred solvents of the prior art, have suitable solvent properties but are not chemically inert. They react with the Δ^{16}-pregnenolones to produce large amounts of the undesirable 16-alkoxy derivatives, thus lowering the yield of the desired products.

I have now discovered that the above-mentioned undesired side reaction can be eliminated and the yield and purity of the desired Δ^{16}-

pregnenolones can be greatly increased by proper choice of the solvent used in step 3 of the process outlined above. Suitable solvents include the tertiary alkanols having not more than six carbon atoms, pyridine and the lower alkyl pyridines. The higher homologs of these soluents are unsuitable because they do not readily dissolve alkali. The suitable solvents can be used in the pure form but their suitability is increased by the addition of not more than about 5% of water. This greatly increases the solubility of alkali in the solvent but at the same time it decreases the solubility of the oxidized pseudosapogenin being treated. Hence, in practice, the optimum amount of water will be found to depend on the solvent, the alkali and the sapogenin used. While any alkali metal hydroxide, carbonate or bicarbonate can be used, I prefer to use potassium hydroxide because of its ready solubility and its high reactivity.

While the reaction mixture may be warmed if desired, I have found that the reaction proceeds rapidly and smoothly at ordinary room temperature and that heating sometimes lowers the yield of the desired product.

It has also been observed that the reaction mixture need not be entirely homogeneous, provided that adequate agitation and mixing is provided. Thus, the entire amount of alkali or oxidized pseudosapogenin need not be dissolved, provided that there is appreciable solubility, because that part which is dissolved will react and be consumed, thus allowing more to be dissolved. In this way the entire amount is soon used up and the overall effect is almost as good as if the mixture had been homogeneous.

Example I

Twenty grams of diosgenin acetate and 100 ml. of acetic anhydride were heated 10 hours at 200° C. in a sealed vessel. After being cooled, the acetic anhydride was distilled in vacuum and the remaining pseudosapogenin was dissolved in 200 ml. of acetic acid to which 5 g. of sodium acetate had been added. A solution of 8 g. of chromium trioxide in 30 ml. of 80% aqueous acetic acid was added dropwise, with agitation and cooling, over a period of 30 minutes and at a temperature of about 15° C. The reaction mixture was then allowed to stand 1 hr. at room temperature, after which an equal volume of water was added, the excess chromic acid was neutralized with 3 g. of sodium bisulfite and the mixture was extracted with ether. After being washed with dilute sodium bicarbonate and with water, the ether solution was evaporated to dryness, leaving a sirupy residue of oxidized pseudosapogenin. This was dissolved in 500 ml. of tertiary-butanol. To this solution was added a solution of 20 g. of potassium hydroxide and 20 g. of water in 500 ml. of tertiary-butanol. The resultant mixture was vigorously stirred at room temperature (25–28° C.) for 3 hr., after which two volumes of water were added and the mixture was extracted with ether. After being washed with water the ether solution was evaporated to dryness and the solid residue was dissolved in 25 ml. of pyridine to which was added 25 ml. of acetic anhydride. After being left overnight the resultant $\Delta^{5,16}$-pregnadien-3β-ol-3-acetoxy-20-one was recovered by diluting with water and extracting with ether. The ether extract was washed with dilute hydrochloric acid, dilute sodium bicarbonate and water; dried with anhydrous sodium sulfate and evaporated to dryness. The crude product thus obtained was purified by dissolving it in benzene and chromatographing it on Florosil (magnesium silicate).

The final product was 10.74 g. of $\Delta^{5,16}$-pregnadien-3β-ol-3-acetoxy-20-one which by ultraviolet assay was found to be 94% pure. Recrystallization from methanol yielded 8.5 g. of substantially 100% pure material. The yield, based on the ultraviolet assay, was 74.5% of the theoretical from diosgenin acetate of 90% purity.

Example II

1.22 g. of purified tigone (oxidized pseudotigogenin acetate) derived from tigogenin acetate was dissolved in 50 ml. of tertiary-butanol to which was added a solution of 2 g. of potassium hydroxide and 2 g. of water in 50 ml. of tertiary-butanol. After agitating the mixture 3 hr. at room temperature it was diluted with an equal volume of water and extracted with ether. The ether solution was washed, dried, and evaporated as in Example I, thus yielding 0.8 g. of Δ^{16}-allopregnen-3β-ol-20-one which assayed 100% pure and amounted to a 100% yield.

Example III

By proceeding substantially as in Example I sarsasapogenin acetate was converted to Δ^{16}-pregnen-3β-ol-3-acetate-20-one.

Example IV

By proceeding substantially as in Example I hecogenin acetate was converted to Δ^{16}-allopregnen-3β-ol-3-acetate-12,20-dione.

Example V

Ten grams of oxidized pseudotigogenin were dissolved in a pyridine solution prepared by shaking 1 liter of pyridine with 1 liter of 5% aqueous potassium hydroxide and discarding the aqueous layer. After being stirred for 3 hr., an equal volume of water was added to the solution and the whole was extracted with ether. The ether extract was washed, dried and evaporated and the product was acetylated and chromatographed as in Example I to yield 3.0 g. of Δ^{16}-allopregnen-3β-ol-3-acetate-20-one.

I claim:

1. In a process for making a Δ^{16}-pregnenolone from a steroidal sapogenin, the steps comprising cleaving an oxidized pseudosapogenin by the action of alkali in a solvent selected from the group consisting of aliphatic tertiary alcohols having not more than six carbon atoms, pyridine and lower alkylpyridines.

2. The process of claim 1 wherein the solvent is tertiary butanol.

3. The process of claim 1 wherein the solvent is pyridine.

4. The process for making a Δ^{16}-pregnenolone from an oxidized pseudosapogenin which comprises treating the oxidized pseudosapogenin with an alkali in a solvent selected from the group consisting of aliphatic tertiary alcohols, pyridine and lower alkylpyridines.

5. The process of claim 4 wherein the alkali is potassium hydroxide.

6. The process of claim 4 wherein the solvent is tertiary butanol.

7. The process of claim 4 wherein the solvent is pyridine.

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No references cited.