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PROCESS FOR CONVERSION OF STEROIDAL SAPOGENINS TO PSEUDOSAPOGENINS

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This invention relates to an improved process for the conversion of steroidal sapogenins to their respective pseudosapogenins, relating particularly to performing the isomerization reaction under milder conditions yet with greatly improved yields.

The isomerization of steroidal sapogenins to pseudosapogenins is a key step in the process of converting such sapogenins to useful steroidal hormones. This isomerization is ordinarily accomplished by heating the sapogenin with acetic anhydride at 200° C. for 10 hours in sealed Carius tubes or in pressure autoclaves. It has been reported that poor results are obtained if the reaction is conducted at temperatures below 200° C. Hence, in the present state of the art the conversion of steroidal sapogenins to pseudosapogenins requires special equipment for performing the reaction at high pressures, yet the yields of pseudosapogenins are often poor, especially for certain specific pseudosapogenins, because of the high temperatures involved.

The isomerization reagent is also an effective acylation agent. In actual practice the first product of the process for making pseudosapogenins are the pseudosapogenin 3,26-diacetates. These diacetates are oily and are rarely isolated. The free pseudosapogenin is obtained in quantitative yield upon alkaline hydrolysis of the pseudosapogenin diacetate. The critical feature in determining the yield of pseudosapogenin recovered is the result of the isomerization reaction. Hence, in subsequent discussions we have sometimes assumed the saponification step to be included and used the terms isomerization and conversion of sapogenin to pseudosapogenin synonymously.

An object of this invention is to provide an isomerization reagent which operates effectively at temperatures under 200° C. and at pressures less than about 45 p. s. i. g.

Another object is to provide an isomerization process which requires no special high pressure equipment.

A further object of this invention is to provide a process in which the isomerization of steroidal sapogenins is performed in consistently high yields regardless of the particular sapogenin being converted to pseudosapogenin.

We have discovered that an isomerization reagent consisting of acetic anhydride containing a small amount of acetic acid converts steroidal sapogenins to their respective pseudosapogenins in high yields at reaction temperatures as low as 160° C. At such temperatures special equipment is not required, the reaction being carried out in ordinary stoppered glass flasks. Conducting the reaction at these temperatures also leads to markedly improved yields of pseudosapogenins, the reaction proceeding almost quantitatively.

Even more surprisingly, we have found that the rate of conversion of individual steroidal sapogenins to their corresponding pseudosapogenin is markedly affected by

the structure of the parent sapogenin and that heating beyond the point of complete conversion gives lower yields of the pseudosapogenins. In particular, differences in the spiroketal side chain configuration of sapogenins is one factor which leads to significant differences in the rate of conversion of the sapogenin to pseudosapogenin. In the accompanying table (Table I) each pair of sapogenins is identical except for isomerism in the spiroketal side chain. The site of isomerism, now considered to be at C^{25} (cf. M. E. Wall, Experientia 11, 340 (1955), for a review of pertinent literature), is immaterial to the present invention. The significance of the data in Table I is that in each pair of normal and iso sapogenins, the normal isomer is converted to its respective pseudosapogenin much more rapidly than is the iso analogue.

TABLE I.—CONVERSION OF NATURAL SAPOGENINS TO PSEUDOSAPOGENINS WITH ACETIC ANHYDRIDE-ACETIC ACID AT 170°

Sapogenin	Side Chain[1] Isomerism	A/B Ring Fusion	Conversion[2] Time, hrs.
Sarsasapogenin	Normal	cis	2
Smilagenin	Iso	cis	6
Neotigogenin	Normal	trans	5
Tigogenin	Iso	trans	21
Yamogenin	Normal	Δ^5	7
Diosgenin	Iso	Δ^5	22

[1] Nomenclature consistent with that given in "Natural Products Related to Phenanthrene," 3rd ed., Fieser and Fieser, p. 587
[2] Time required for about 90% or more of isomerization.

We have also found that differences in configuration at C^5 can also affect the rate of conversion of sapogenin to pseudosapogenin. The data of Table I illustrate this influence is in the order of $C^5cis > C^5trans > C\Delta^5$.

According to the present invention sapogenins are converted to their respective pseudosapogenins by a process comprising heating the sapogenin in acetic anhydride containing a small amount, preferably about 0.1 to 1% volume to volume basis, of acetic acid at temperatures below 200° C., preferably at about 170–180° C., until the isomerization is substantially complete, hydrolyzing the resulting pseudosapogenin diacetate to pseudosapogenin, and recovering the pseudosapogenin.

Although we usually use a ratio of 2.5 parts of acetic anhydride containing acetic acid to one part of sapogenin, this ratio is not critical to the practice of the invention. Both higher and lower ratios of acetic anhydride-acetic acid to sapogenin have been used successfully.

The quantity of acetic acid added to the acetic anhydride can also be varied to give concentrations lower than and substantially higher than the preferred concentration of about 0.1 to 1% by volume without affecting significantly the improvement of the present invention.

While the acetic anhydride-acetic acid reagent is effective in converting sapogenins to pseudosapogenins over a temperature range of 160 to 200° C., temperatures of about 170 to 180° C. are preferred. At these temperatures the reactions can be performed in stoppered glass flasks, the rate of isomerization is satisfactory, and the yields of pseudosapogenin are high.

The following examples are presented in illustration of the present invention.

EXAMPLE 1

Conversion of sarsasapogenin to pseudosarsasapogenin

Sarsasapogenin, 10.0 grams, and 25 ml. of acetic anhydride containing 0.1% by volume acetic acid were added to a 250 ml. round bottom flask. The flask was securely stoppered with a glass stopper. The contents of the flask were heated at 170° C. for two hours. The acetic anhydride was then removed in vacuo and the

residue saponified by refluxing in 200 ml. of methanol containing 20.0 grams of potassium hydroxide. On dilution with water a copious precipitate of pseudosapogenin was obtained. The precipitate was washed thoroughly with water, dried, and recrystallized from ethyl acetate to give 8.5 grams of pseudosarsasapogenin, M. P. 169–173° C. Paper chromatography showed that the ethyl acetate mother liquors contained essentially pseudosarsasapogenin so that the conversion was actually better than the indicated 85%.

EXAMPLE 2

Conversion of smilagenin to pseudosmilagenin

Smilagenin, 10.0 grams, was heated 6 hours at 170° C. with 25 ml. of acetic anhydride containing 0.1% acetic acid. Following the procedures described in Example 1, pseudosmilagenin was recovered. Recrystallization from ethyl acetate gave 8.8 grams of pseudosmilagenin, M. P. 161–162° C.

EXAMPLE 3

Conversion of diosgenin to pseudodiosgenin

In general, the procedure of Example 1 was followed. Isomerization in acetic anhydride containing 0.1% acetic acid was conducted at 180° C. for 10 hours. From 10 grams of diosgenin there was obtained 9.0 grams of pseudodiosgenin, M. P. 157–167° C.

EXAMPLE 4

Conversion of tigogenin to pseudotigogenin

Tigogenin, 10.0 grams, was heated at 160° C. for 30 hours in 25 ml. acetic anhydride containing 0.1% acetic acid. Following the procedures of Example 1, 7.8 grams of pseudotigogenin, M. P. 170–180° C., was recovered.

EXAMPLE 5

Conversion of hecogenin to pseudohecogenin

Using the isomerization conditions of Example 4, from 10.0 grams of hecogenin there was recovered 9.1 grams of pseudohecogenin, M. P. 189–195° C.

EXAMPLE 6

Using procedures similar to those of preceding examples, 11-oxo-tigogenin and 11-oxo-diosgenin were converted to their pseudo analogues. Identification verified by comparison of infrared spectra with those of authentic pseudo compounds.

We claim:

1. A process for converting a steroidal sapogenin to its pseudosapogenin comprising heating said sapogenin in acetic anhydride containing about 0.1 to 1.0% by volume of acetic acid, at temperatures in the range of about 160 to 180° C., until the isomerization of the sapogenin to its pseudo form is substantially complete.
2. The process of claim 1 in which the sapogenin is sarsasapogenin.
3. The process of claim 1 in which the sapogenin is smilagenin.
4. The process of claim 1 in which the sapogenin is diosgenin.
5. The process of claim 1 in which the sapogenin is hecogenin.
6. The process of claim 1 in which the sapogenin is tigogenin.
7. The process of claim 1 in which the sapogenin is 11-oxo-tigogenin.
8. The process of claim 1 in which the sapogenin is 11-oxo-diosgenin.

References Cited in the file of this patent

Marker: J. A. C. S. September 1947, pages 2170, 2184, 2191, 2194, 2196.