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SAPOGENIN DERIVATIVES AND PREPARATION OF SAME

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No Drawing. Original application May 15, 1941, Serial No. 393,666. Divided and this application May 24, 1944, Serial No. 537,196

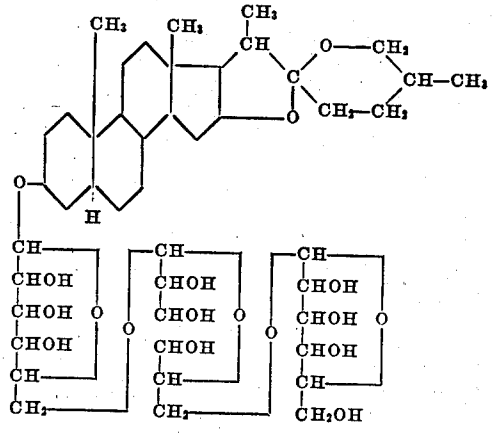
5 Claims. (Cl. 260—210)

The invention relates to the preparation of steroidal compounds, and this application is a division of our copending application, Serial No. 393,666, filed May 15, 1941, now Patent No. 2,352,851, issued July 4, 1944.

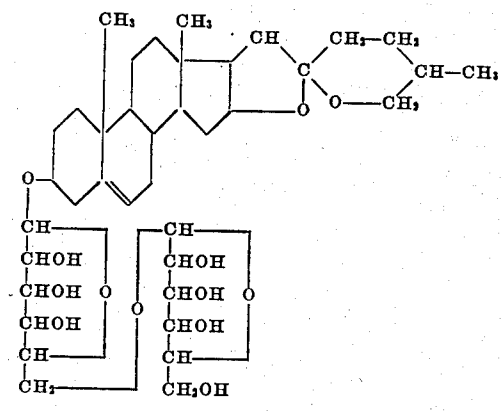
This application relates more particularly to the preparation of glycosidic derivatives of pseudo-sapogenin compounds unacylated at least at the exo-hydroxyl group and in the sugar residues, oxidizing said derivatives in the side chain attached to ring D and hydrolyzing the oxidation product to obtain Δ^{16}-20-keto compounds having hydroxyl groups in place of the sugar residues.

According to this invention, the pseudo-sapogenins or their ring A and/or B glycosidic derivatives are prepared by reacting glycosidic derivatives of the sapogenins with acidic agents, for example, acylating agents such as acid anhydrides, under conditions more vigorous than those required merely for acylation.

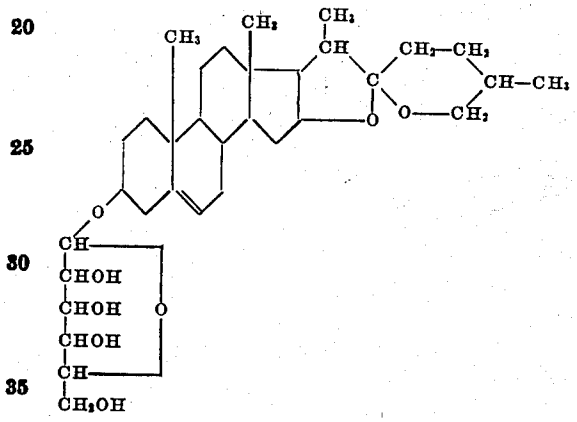
By glycosidic derivatives of the sapogenins we means sapogenin derivatives in which sugar residues are attached through a hemi-acetal linkage to the cyclopentanoperhydrophenanthrene nucleus. In general, the exact nature of the structures of these substances are not known with certainty. The following formulae illustrate various types of the above sapogenin glycosides:



VIII. Sarsasaponin



IX. Trillarin



X. Trillin

Generally speaking the glycosides of the steroidal sapogenins may be classified as (1) saponins; (2) simpler glycosides. The former usually contain from three to six sugar units, all of which may be the same, or they may be different. The most commonly occurring sugar units are those of glucose, galactose, rhamnose, and xylose. The simpler glycosides differ from the saponins in that (1) they contain fewer, i. e., one to three, sugar units; (2) they are more readily obtained crystal-

line; (3) they do not show marked capillary active properties. In most cases, including the compounds represented by VIII, IX, and X, the exact nature of the glycosidic linkages is not definitely known; that is, it is not known whether the sugars have a furanose or pyranose structure, nor which carbon atoms of the different sugar units are (through oxygen) united. In many cases even the number and kind of sugar units present are not known.

See further, Fieser, Chemistry of Natural Products Related to Phenanthrene, 2nd ed., p. 333 ff. (Reinhold Publishing Corporation, New York city, 1937).

Since the steroidal sapogenins occur in nature, not in the free form, but combined with sugar units as glycosidic derivatives, the present invention makes it unnecessary to isolate the sapogenins. Instead, their more readily available glycosides may be converted directly to pseudo-sapogenin derivatives. This elimination of a formerly essential step results in higher yields of steroidal hormones from plant sources.

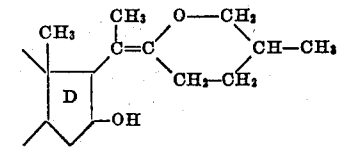
As naturally occurring glycosidic derivatives of steroidal sapogenins which may be used in the practice of this invention, there may be mentioned amolonin, sarsasaponin, digitonin, or like steroidal saponins. Also, there may be used partially degraded glycosidic derivatives of these saponins, such as trillarin or trillin. Such partially degraded glycosidic derivatives of saponins are obtained by hydrolyzing the saponin at some of the oligosacharide linkages by means of enzymes or dilute acids or similar reagents. Again, there may be used synthetic glycosidic derivatives of steroidal sapogenins such as the synthetic galactosides, glucosides, ribosides, and other glycosides of sapogenins such as sarsasapogenin, diosgenin, or other steroidal sapogenins containing reactive nuclear hydroxyl groups. Synthetic glycosides suitable for the practice of this invention may also be prepared from sapogenins which have reactive nuclear hydroxyl groups, but which are not agly cones of naturally occurring saponins. For example, although neither epi-sarsasapogenins nor its glycosides occur in nature, glycosides of epi-sarsasapogenin may be prepared synthetically from sarsasaponin by converting the latter into its aglycone, sarsasapogenin, and then converting this into epi-sarsasapogenin. The epi-sarsasapogenin may then be treated to form the glycoside as for example by treatment with bromoacetoglucose.

The conversion of the glycosidic derivative of the steroidal sapogenin into an acylated glycosidic pseudo-sapogenin may be effected by treating the former with an acylating agent under conditions more vigorous than those required for mere acylation. This step may be effected, for example, by treatment of the glycosidic derivatives of the sapogenins with a carboxylic anhydride at 175–250° C. We have found that best results are obtained with lower fatty acid anhydrides while maintaining the reaction temperature in the neighborhood of 200° C. The product thus formed is an acylated glycosidic pseudo-sapogenin derivative acylated at least at the exo-hydroxyl group and in the sugar residues.

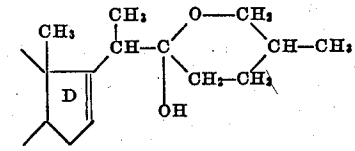
The acylated glycosidic pseudo-sapogenin derivatives may be hydrolyzed with alkaline reagents with production of a glycosidic derivative of a pseudo-sapogenin unacylated at least at the exo-hydroxyl group and in the sugar residues.

The pseudo-sapogenins are characterized by the fact that they contain a new type of side chain which undergoes distinctive reactions. Thus the pseudo-sapogenins are unsaturated to bromine and therefore readily decolorize a solution of bromine in acetic acid. On treatment with acids, for example, with alcoholic hydrochloric acid, the pseudo-sapogenins are isomerized to the corresponding steroidal sapogenins. The side chain of the pseudo-sapogenins contains a reactive hydroxyl group which may be acylated, for example, acetylated.

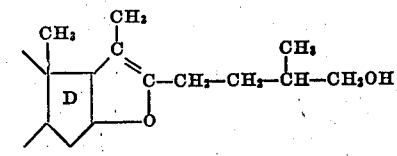
It is believed that the properties of pseudo-sapogenins are best explained if the side chain attached to ring D of the cyclopentanoperhydrophenanthrene nucleus be represented by one of the following partial formulae:



I.



II.

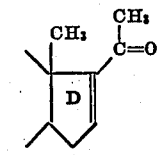


III.

Of these formulae, III seems to account best for the transformations described in the present invention. It will be observed that the partial formulae I, II and III all contain a reactive hydroxyl group. The prefix exo in the term exo-hydroxyl group has the same significance that it does in other branches of organic chemistry, namely, that the particular function involved is exterior to a ring system and in a position not known with greater certainty.

The glycosidic derivative of a pseudo-sapogenin unacylated at least at the exo-hydroxyl group and in the sugar residues is then mildly oxidized in the side chain attached to ring D, thus producing an oxidation product in which the sugar residues are not acylated.

This oxidation product, which is a new intermediate compound, is subjected to hydrolysis with an acidic reagent with production of a steroid having in ring D the structure



and having in the remainder of the steroid skeleton hydroxyl groups in place of the sugar residue.

The step of oxidation referred to in the above description is best accomplished under relatively mild conditions. We have found that best results are obtained if the pseudo-sapogenin derivatives are oxidized below 50° C. by means of an oxidizing agent of the class consisting of chromic and permanganic acids and their salts. However, other

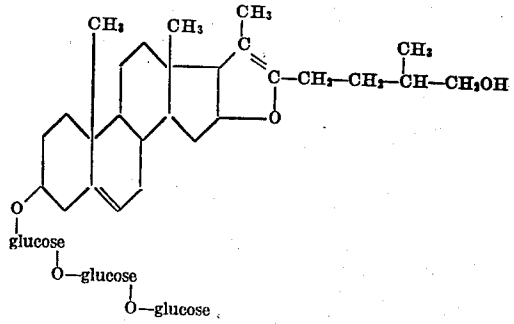
oxidizing agents such as ozone, hydrogen peroxide, and the like may effectively be employed in this step. Particularly satisfactory results are obtained when the oxidation is conducted at 20–35° C. in acetic acid, using chromic anhydride as the oxidant.

Suitable reagents for the alkaline hydrolysis previously described are cold sodium methylate solution, barium hydroxide solution, calcium hydroxide solution and cold sodium hydroxide solution. The acidic hydrolysis required to remove the sugar residues from the steroid nucleus is best achieved by boiling the substance with alcoholic hydrochloric acids. However, other acidic reagents such as dilute sulfuric acid, or other mineral acids may be used instead.

Our invention may be further illustrated by the following examples.

Example 1

The saponin from *Trillium erectum* is obtained and converted into the acetate of *Trillium erectum* pseudo-saponin as described in our application, Serial No. 393,666. This product is then hydrolyzed with alkaline reagents as above described, producing a compound unacylated at the exo-hydroxyl group and in the sugar residues and having the following formula



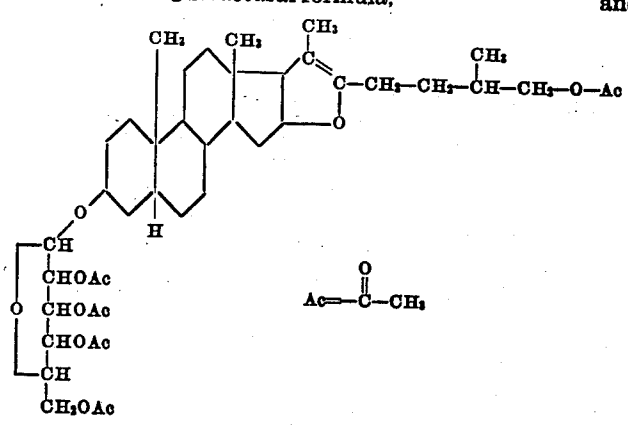
This product is then oxidized as above described and the oxidation product is hydrolyzed with acidic reagents also as described above, producing $\Delta^{5,16}$-pregnadienol-3-(β)-one-20.

Example 2

Pseudo-trillin acetate is prepared as described in application, Serial No. 393,666. It is then hydrolyzed with alkaline reagents, oxidized and hydrolyzed with acidic reagents as described above to produce $\Delta^{5,16}$-pregnadienol-3-(β)-one-20.

Example 3

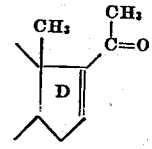
Pseudo-sarsasapogenin-α-glucoside penta-acetate is prepared as described in application, Serial No. 393,666. This substance may be represented by the following structural formula,



It is then hydrolyzed with alkaline reagents to remove the acetyl groups, all as described above, to produce the corresponding 3-hydroxy-Δ^{16}-20-keto compound.

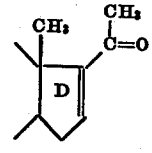
What we claim as our invention is:

1. The process which comprises subjecting a glycosidic derivative of a pseudo-sapogenin unacylated at the exo-hydroxyl group, to mild oxidation in the side chain attached to ring D, and subjecting the oxidation product to hydrolysis with an acidic agent, with production of a steroid having in ring D the structure



and having in the remainder of the steroid skeleton, hydroxyl groups in place of the sugar residues.

2. The process which comprises oxidizing below 50° C. a glycosidic derivative of a pseudo-sapogenin unacylated at the exo-hydroxyl group by means of an oxidizing agent of the class consisting of chromic and permanganic acids and their salts, and subjecting the oxidation product to hydrolysis with an acidic agent, with production of a steroid having in ring D the structure

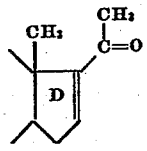


and having in the remainder of the steroid skeleton, hydroxyl groups in place of the sugar residues.

3. The process which comprises subjecting a glycosidic derivative of a pseudo-sapogenin unacylated at least at the exo-hydroxyl group and in the sugar residues to mild oxidation in the side chain attached to ring D thereby obtaining an oxidation product having an unacylated sugar residue attached to the steroid nucleus.

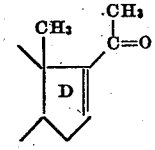
4. The process for the preparation of steroidal compounds which comprises subjecting a glycosidic derivative of a pseudo-sapogenin acylated at least at the exo-hydroxyl group and in the sugar residues to hydrolysis with an alkaline reagent, with production of a glycosidic derivative of a pseudo-sapogenin unacylated at least at the exo-hydroxyl group and in the sugar residues, mildly oxidizing said glycosidic pseudo-sapogenin derivative in the side chain attached to ring D, and subjecting the oxidation product to hydrol-

ysis with an acidic reagent, with production of a steroid having in ring D the structure



and having, in the remainder of the steroid skeleton, hydroxyl groups in place of the sugar residues.

5. The process for the preparation of steroidal compounds which comprises isomerizing and acylating the side chain attached to ring D of a glycosidic derivative of a steroidal sapogenin by reacting said glycosidic derivative with an acylating agent under conditions more vigorous than those required for mere acylation, with production of a glycosidic derivative of a pseudo-sapogenin acylated at least at the exo-hydroxyl group and in the sugar residues, subjecting said acylated glycosidic pseudo-sapogenin derivative to hydrolysis with an alkaline reagent, with production of a glycosidic derivative of a pseudo-sapogenin unacylated at least at the exo-hydroxyl group and in the sugar residues, mildly oxidizing said glycosidic pseudo-sapogenin derivative in the side chain attached to ring D, and subjecting the oxidation product to hydrolysis with an acidic reagent, with production of a steroid having in ring D the structure



and having, in the remainder of the steroid skeleton, hydroxyl groups in place of the sugar residues.

RUSSELL EARL MARKER.
HARRY MEANS CROOKS, JR.
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