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PREPARATION OF 7-DEHYDRO STEROLS

Hans R. Rosenberg, Wilmington, Del., assignor to E. I. du Pont de Nemours & Company, Wilmington, Del., a corporation of Delaware

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This invention pertains to the preparation of organic compounds containing a cyclo-pentano-perhydro-phenanthrene nucleus. More particularly it pertains to the preparation of such compounds from Δ^5-7-hydroxy-steroid esters. Still more particularly, it relates to the removal of acid groups from Δ^5-7-hydroxy-steroid esters whereby Δ^5,7-dehydro-steroid compounds are formed. In one of its preferred embodiments, it pertains to the preparation of 7-dehydro sterol monocarboxylic acid esters and 7-dehydro sterols from Δ^5-7-hydroxy-sterol monocarboxylic acid esters. The invention also relates to novel procedural conditions, assistants and processes for preparing such 7-dehydrosteroid compounds.

The thermal decomposition of diesters of certain 7-hydroxy-steroids, namely, diesters of 7-hydroxy-sterols and monocarboxylic acids, at reduced pressures has been described in U. S. P. 2,098,984. Under the conditions specified therein small yields of 7-dehydro-sterol esters are formed. 7-dehydro-sterol esters and 7-dehydro-sterols have also been prepared from such diesters of steroids by treatment with organic nitrogenous bases such as organic amines until an acid group has been removed. See U. S. P. 2,209,934. The 7-dehydro esters are then saponified to yield 7-dehydro sterols. The use of oxonium salt forming compounds in the place of all or part of such bases with or without additional assisting agents in addition has been described in U. S. P. 2,255,815.

While these above described processes have some utility, they have some commercial disadvantages and could be improved upon. The thermal decomposition at elevated temperatures, for instance, requires very careful supervision. Furthermore, the use of a high degree of vacuum interposes economic and practical difficulties of operation. In addition, the heating of the ester melt causes decomposition of useful products into those of no economic value.

The organic nitrogen bases and oxonium salt forming compounds have utility but are somewhat expensive and are sometimes difficult to obtain.

This invention has for an object the provision of new and practical processes for producing 7-dehydro-steroid compounds. A further object is the provision of processes of forming 7-dehydro-steroid compounds which eliminate uneconomic by-product formation. Another object is to provide processes for making 7-dehydro-steroid compounds which can be carried out in simple and economical apparatus. Another object is to produce 7-dehydro-steroid compounds in increased yields. Still other objects are to provide novel processes of removing acid groups from esterified Δ^5-7-hydroxy-steroid compounds and to promote a general advance in this art.

The above objects are accomplished and the above disadvantages of prior art processes overcome by the invention hereinafter described.

It has been found according to one aspect of the invention, that 7-dehydro-steroids can be obtained in increased yields by heating Δ^5-7-hydroxy-steroid esters in a liquid hydrocarbon medium containing certain assisting agents. The heating is continued until a material amount of acid has been removed from the esters. The acid formed is then separated from the reaction mixture and the 7-dehydro-steroid compounds further processed.

In a more limited sense, it has been found that the decomposition reaction of selectively splitting out one mol of acid, especially an organic monocarboxylic acid, from Δ^5-7-hydroxy-steroid esters by utilizing a liquid hydrocarbon medium, can be accelerated by a number of assisting agents which possess the following characteristics: (*a*) they are essentially insoluble in the solvent used, (*b*) they are non-destructive of Δ^5-7-hydroxy-steroid esters and (*c*) they possess an active surface.

In a further, more specific aspect of the invention it has been found that 7-dehydro-steroid compounds can be made by heating Δ^5-7-hydroxy-steroid esters in a liquid medium containing at least one assisting agent having the above-described general properties, but which is further characterized in that it is insoluble in the liquid medium, solid and porous. Suitable materials of the last mentioned type include, solid water-insoluble metal powders, active or activated carbons including activated charcoals and active carbon, metal oxides, carborundum, powdered glass, silica gels, etc.

The last mentioned embodiment of the invention is not limited to the use of liquid hydrocarbon media. Various other solvents or diluents which are non-destructive of 7-dehydro-steroid esters and steroids may be used in place of or in admixture with such hydrocarbon media. The useful solvents may be acid binding agents or assist in the removal of acid groups from Δ^5-7-hydroxy-steroid esters. Among these useful solvents are organic nitrogen bases such as amines and oxonium salt forming compounds; suitable compounds of each of these classes are set forth in U. S. patents, 2,209,934 and 2,255,815.

Referring now to the hydrocarbon media aspects of the invention, it has been found that the splitting out of organic acid groups from esteri-

fied 7-hydroxy-steroid compounds can be accelerated by the use of inorganic salts which have a pH range in water between 5 and 12 and metal oxides in addition to the solid water-insoluble, porous, active-surface assisting agents described above.

In order to determine whether a compound meets with the requirements for an assisting agent as outlined above, the following simple tests should be carried out.

(a) Test for insolubility

The compound to be tested should be mixed with the solvent to be used and heated to about 100° C. If the compound to be tested is essentially insoluble, it conforms with the insolubility requirement of the class of assisting agents.

(b) Tests for destructive properties

Two milligrams of ergosterol or a similar compound are heated in the presence of the compound to be tested and a hydrocarbon, for example, cyclohexane, in a sealed tube to 200° C. for one hour. The reaction product is diluted with ethyl alcohol and spectroscopically examined for the presence of ergosterol bands. The compounds in question is suitable if the ergosterol is not destroyed.

(c) Test for active surface properties

The compound to be tested as assisting agents should be added in small amounts to carbonated water. If the compound to be tested has surface active properties, carbon dioxide gas evolves at a high speed, whereas when the compound to be tested has no or only slight surface active properties, no or only a small amount of carbon dioxide evolves.

The beneficial action of the assisting agents determined by the above test is quite surprising, unexpected and difficult to explain. It is possible that physical as well as chemical phenomena are involved. The beneficial effect of the agents is illustrated in the following exemplary procedures:

When 7-hydroxy-cholesterol-dibenzoate is heated in cyclohexane at 183° C. for 75 minutes followed by saponification of the reaction product, a yield of about 1% 7-dehydro-chloesterol is obtained. On the other hand when the same reaction is carried out in the presence of aluminum oxide, a yield of 10–12% 7-dehydro-chloestrol is obtained. When the same reaction mixture is heated to 200° C. for 14 hours, about 46% 7-dehydro-cholestrol is obtained without using assisting agents, while in the presence of sodium chloride, 70–80% 7-dehydro-cholesterol is obtained.

The invention will be further illustrated but is not intended to be limited by the following examples:

Example I

7-hydroxy-cholesterol-dibenzoate is dissolved in cyclohexane in a molecular ratio of 1:40 and an equimolecular amount of sodium carbonate added. The mixture is heated for 2 hours at 200° C. in a closed system. After cooling the reaction product is extracted with an aqueous solution of sodium carbonate to remove the benzoic acid formed. To the remaining cyclohexane solution a solution of potassium hydroxide and alcohol is added and the mixture refluxed for one hour in order to saponify the 7-dehydro-cholesterol-benzoate which has been formed. The saponification mass after cooling is extracted with water and the remaining cyclohexane solution subjected to distillation until only a small amount remains. The residue is cooled whereby 7-dehydro-cholesterol crystallizes out. A yield of 32% of 7-dehydro-cholesterol is obtained.

Example II

7-hydroxy-cholesterol-dibenzoate is dissolved in cyclohexane in a molecular ratio of 1:40 and an equimolecular amount of sodium chloride is added. The mixture is heated in a sealed system for 8 hours at 200° C. The reaction product is filtered from the sodium chloride after cooling and the benzoic acid formed during this reaction is extracted with an aqueous sodium hydroxide solution. From the remaining cyclohexane solution, 7-dehydro-cholesterol-benzoate is obtained in a yield of 75–80% after the manner set forth in Example I.

The same reaction, using tetralin (tetrahydronaphthalene) instead of cyclohexane, and refluxing the mixture for 2 hours, gave a yield of 60–65.%

Example III

7-hydroxy-cholesterol-dibenzoate is dissolved in cyclohexane and carborundum is added as an assisting agent. The reaction mixture is heated to 200° C. for 14 hours in a closed system. The reaction product is then worked up according to the procedure outlined in Example I whereby a yield of 82% of 7-dehydro-cholesterol-benzoate is obtained.

Example IV

7-hydroxy-cholesterol-dibenzoate is dissolved in cyclohexane and copper powder is added. The mixture is heated to 200° C. in a sealed system. The reaction product is worked up as described in Example I. A yield of 50–60% of theory of 7-dehydro-cholesterol-benzoate is obtained.

Example V

Three parts of 7-hydroxy-cholesterol-dibenzoate and 3 parts of activated charcoal are mixed with 20 parts of cyclohexane and are heated in a sealed system to 150° C. for 2 hours. After cooling, the reaction product is filtered from the charcoal which in turn is extracted with ether. The combined extracts are washed with sodium carbonate solution to remove benzoic acid. After drying over sodium sulfate the solution is concentrated and to the concentrate, acetone is added. 7-dehydro-cholesterol-benzoate crystallizes out. Yield=58.3%.

Example VI

Three parts of 7-hydroxy-cholesterol-dibenzoate, 3 parts of carborundum and 25 parts of dioxane are heated in a sealed tube to 190° C. for 1.5 hours. After cooling, the solution is filtered from the carborundum and poured in water. The water solution is extracted with methylene chloride and the methylene chloride solution washed with an aqueous sodium carbonate solution. The methylene chloride is distilled off and acetone added to the residue. 1.7 parts of 7-dehydro-cholesterol-benzoate are obtained which correspond to a yield of 69% of theory.

Example VII

Three parts of 7-hydroxy-cholesterol-dibenzoate, 3 parts of carborundum and 25 g. of pyridine are heated in a sealed system to 190° C. for 1.5 hours. After cooling, the mixture is filtered and the filtrate poured on ice and water and ex-

tracted with ether. The ether solution is washed consecutively with dilute hydrochloric acid, diluted alkali and water until neutral. After drying over sodium sulfate, the ether is distilled off and acetone added to the residue. 7-dehydro-cholesterol-benzoate crystallizes out in a yield of 55% of theory.

It should be understood that the invention is not limited to the treatment of the specific 7-hydroxy-sterol esters described in the working examples. On the contrary, it embraces the treatment of steroids generally wherein a double bond exists in a position adjacent to the esterified hydroxy group in the 7-position, regardless of whether additional substituents are also present in other positions in the molecule. Any ester compounds having the cyclo-pentano-perhydrophenanthrene skeleton may be used wherein the ester group is in the 7-position and a double bond in the 5,6-position. Such substances are sometimes termed steroid or sterid compounds and include those having the nucleus referred to with or without side chains including said chains with other functional groups such as oxo, hydroxyl and carboxyl groups and their derivatives. Thus, the term "steroids" includes not only sterols, but also bile acids, plant heart poisons, saponines and sex hormones. Among the suitable polyesters of the above-described types are esters of β-7-hydroxy-cholesterol, 7-hydroxy-sitosteryl diesters, 7-hydroxy stigmasterol diester, 3,7-dihydroxy-5-cholenic acid esters, Δ 5-andro-stentriol-3,7,17-triesters, and the corresponding esters of pregnane series. Still other suitable esters include the simple or mixed carboxylic esters of 7-hydroxy sterol compounds obtainable from acids such as nitrobenzoic, m-dinitrobenzoic, chlorobenzoic, toluic, phenylacetic, cinnamic, formic, acetic, propionic, butyric, valeric, etc. acids and their acid anhydrides and acid halides, e.g. acyl chlorides. Any of the diesters disclosed in U. S. patents, Nos. 2,209,923 and 2,215,727, for instance, may be used as starting materials in the present processes.

In place of the specific hydrocarbons set forth in the above examples there may be substituted a wide variety of hydrocarbons which are stable and do not polymerize or react with the components of the reaction media at reaction temperatures, having the above-described characteristics. The useful hydrocarbons are not limited to any one particular type, on the contrary, simple and mixed aliphatic including cyclo-aliphatic, alicyclic, aromatic and aliphatically substituted aromatic hydrocarbons can be used. The hydrocarbons may be substituted by innocuous groups such as chlorine, fluorine, etc. Preferred hydrocarbons are stable, normally liquid and liquid at atmospheric pressure at temperatures in excess of 150° C.

As examples of suitable additional stable hydrocarbons mention is made of methylcyclohexane, ethylcyclohexane, benzene toluene, xylene, naphthalene, dihydronaphthalene, decahydronaphthalene; pinene; heptane, octane, etc., petroleum, ether, benzine, ligroin and similar mineral oil fractions, etc.; halogenated hydrocarbons, e. g. dichloroethane, tetrachloroethane, chlorobenzene, dichlorobenzenes, chlorotoluene, benzotrifluoride, etc.

The quantity of hydrocarbon may be varied over a fairly wide range, e. g. from 1 to 100 parts of hydrocarbon per part of steroid ester. In general, higher yields are obtained by the use of an excess of hydrocarbon. A preferred range is 5 to 25 parts of hydrocarbon per part of steroid ester.

The temperature and time may also be varied over a fairly wide range, e. g. from 150° C. and less to 300° C. and over. A temperature from 160° C. to 260° C. represents a preferred range. The time may vary from about 2 hours to 16 hours and over depending somewhat on the temperatures employed. For example, 2 hours' heating at 220° C., 6 hours at 200° C., and 16 hours at 180° C., give substantially the same yields. It is not necessary, however, to convert all the diester to the 7-dehydro compound. The reaction may be cut short when partially complete. It may be conducted somewhat continuously by drawing off and crystallizing formed 7-dehydro compounds and replenishing the reaction mixture.

Among the additional metal salts useful in the process which in 10% water solution have a pH between 5 and 12 inclusive are sodium acetate, sodium phosphate, potassium chloride, potassium bromide, potassium acetate, potassium phosphate, sodium arsenite, etc. One or more of such salts can be used in hydrocarbon media.

Various other solid water-insoluble assisting agents which have a large amount of surface area may be substituted in like manner for the carborundum, copper powder and charcoal of the examples. Suitable specific agents include aluminum oxide, zinc oxide, silver oxide, copper oxide, silica dioxide, magnesium oxide, blood charcoal, bone charcoal, aluminum powder, zinc powder, tin powder, etc.

The amount of assisting agent may vary over a wide range. In general, an equimolecular amount should be used. However, amounts from ½ mol to 10 mols may be used if desired.

The novel procedures hereof constitute an important advance in the art. They find especial usefulness in the production of provitamins D from Δ^5-7-hydroxy-sterol esters. The yields are definitely superior to those of the prior art.

The use of the novel assisting agents of this invention has a number of advantages, the most important of which is the fact that it enables one to obtain increased yields of Δ^5-7-dehydro-steroid products. An additional advantage resides in the fact that the assistants are readily available. A still further advantage resides in the fact that the assistants are less costly than the acid binding agents previously proposed. The hydrocarbon media has some advantages also in that they are inexpensive, readily available, and enable clear colored products to be prepared. The highly porous activated surface assisting agents enable the reaction to be carried out at a materially lower temperature which prevents decomposition and has many other economic advantages.

As many apparently widely different embodiments of this invention may be made without departing from the spirit and scope thereof, it is to be understood that I do not limit myself to the specific embodiments herein except as defined by the appended claims.

I claim:

1. The process which comprises admixing an esterified 7-hydroxy sterol with a stable hydrocarbon having a boiling point between 150° C. and 250° C. having suspended therein as an assisting agent finely divided silicon carbide to a temperature between 100° C. and 300° C. for a period of at least one hour, extracting the acid produced and recovering a 7-dehydro sterol compound.

2. A process for thermally decomposing a diester of 7-hydroxy-cholesterol which comprises dissolving said diester in a stable hydrocarbon solvent having a boiling point between 150° C. and 250° C. and heating the resulting solution, while maintaining the temperature thereof uniform by suspending therein finely divided, insoluble heat-transferring particles.

3. A process for thermally decomposing 7-hydroxy-cholesterol-dibenzoate which comprises dissolving said compound in a stable hydrocarbon solvent having a boiling point between 150° C. and 250° C. and heating the resulting solution, while maintaining the temperature thereof uniform by suspending therein finely divided, insoluble heat-transferring particles.

4. A process for thermal decomposing 7-hydroxy-cholesterol-dibenzoate which comprises dissolving said compound in cyclohexane and heating the resulting solution, while maintaining the temperature thereof uniform by suspending therein finely divided, insoluble, heat-transferring particles.

HANS R. ROSENBERG.