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PROCESS FOR PRODUCING STEROL DERIVATIVES

Walter C. Meuly, Highland Park, N. J., and Hans R. Rosenberg, Wilmington, Del., and Daniel H. Terry, Woodstown, N. J., assignors to E. I. du Pont de Nemours & Company, Wilmington, Del., a corporation of Delaware

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This invention relates to new and improved processes for producing 7-dehydro-sterols and in particular it refers to processes for the production of 7-dehydro-cholesterol from 7-hydroxy-cholesterol-3-monoesters.

It is known that 7-dehydro-cholesterol may be produced from 7-hydroxy-cholesterol-3-monoesters by producing the diester of the 7-hydroxy-cholesterol with monocarboxylic acids and then thermally decomposing said diester at elevated temperatures and under reduced pressures in order to form 7-dehydro-cholesterol-3-monoesters. This latter product is then saponified to produce the desired 7-dehydro-cholesterol. A reaction of this type is described in U. S. Patent No. 2,098,984.

It should be noted, however, that the foregoing reaction requires three steps, namely, conversion of the 3-monoester to the 3,7-diester, then thermal decomposition of the diester, and finally saponification to remove the 3-monoester radical.

It is an object of this invention to eliminate one of the steps in the foregoing prior art process and produce 7-dehydro-cholesterol and related sterol derivatives by a new and improved process. A further object is to produce these products by a simple and direct process which eliminates the necessity of obtaining diesters. A still further object is to produce 7-dehydro-sterols by direct dehydration of 7-hydroxy-sterol-3-monoesters. A still further object is to accomplish this dehydration in a simple and inexpensive manner, which results in the production of high yields of the 7-dehydro-sterols. Additional objects will become apparent from a consideration of the following description and claims.

These objects are obtained in accordance with the invention to be described herein wherein 3-monoesters of 7-dehydro-sterols having a double bond in 5,6-position are produced by dehydrating a 7-hydroxy-sterol-3-monoester having a double bond in 5,6-position. In a more restricted sense this invention is concerned with the production of 7-dehydro-cholesterol by the dehydration of 7-hydroxy-cholesterol-3-monoesters and the saponification of the resulting 7-dehydro-cholesterol-3-monoester. In a still more restricted sense this invention pertains to the foregoing process wherein the desired dehydration is carried out with either a liquid or a solid dehydrating agent. In its preferred embodiment this invention concerns the production of 7-dehydro-cholesterol by dehydrating at elevated temperatures and with either a liquid or a solid dehydrating agent, 7-hydroxy-cholesterol-3-monobenzoate, then saponifying the resulting 7-dehydro-cholesterol-3-monobenzoate.

In accordance with the present invention the dehydration of the 7-hydroxy-sterol-3-monoester is conducted in either the liquid phase or in the solid phase. By "liquid phase" is meant a reaction in a liquid, either with or without a dehydrating agent which does not destroy the resulting provitamin. Agents of this type are, for example, hydrocarbons, alcohols, amines, etc. By "solid phase" is meant a reaction in the absence of any liquid, and with or without a solid dehydrating agent which does not destroy the resulting provitamins. Solid dehydrating agents are, for example, metal oxides, salts, acyl or aryl sulphone chloride, metallic carbides and the like. When this dehydrating reaction is conducted in the absence of either liquid or solid dehydrating agents it is generally not as satisfactory as when those agents are present, and results in inferior yields.

Dehydration of 7-hydroxy-sterol-3-monoesters as aforesaid splits water from the 7,8-position to form 7-dehydro-sterol-3-monoesters. As mentioned previously, these 3-monoesters may then be saponified to form 7-dehydro-sterols. In the case of the dehydration of 7-hydroxy-cholesterol-3-monoesters the reaction product is 7-dehydro-cholesterol-ester and this latter product may be saponified to form 7-dehydro-cholesterol, which is provitamin D_3.

The invention may be more readily understood by a consideration of the following illustrative examples wherein the quantities are stated in parts by weight.

Example 1

Two parts of 7-hydroxy-cholesterol-3-monobenzoate, M. P. 192–194° C. (described by Rosenberg and Tinker, U. S. P. 2,215,727) is heated for two hours at 200° C. under nitrogen. The residue is then taken up in 100 parts of acetone, cooled to room temperature, and the insoluble material filtered off. 7-dehydro-cholesterol-benzoate is obtained in a 10% yield of theory and on saponification with alcoholic-caustic is converted into 7-dehydro-cholesterol.

Example 2

A mixture of 2 parts of 7-hydroxy-cholesterol-3-monobenzoate and 25 parts of distilled dimethyl aniline is refluxed under nitrogen for three hours. After cooling, the dimethyl aniline is distiled under reduced pressure and the residue is taken up in 80 parts of acetone. On cooling 0.73 part (38% of theory) of 7-dehydro-cholesterol-3-benzoate is obtained, which is converted by saponification into 7-dehydro-cholesterol.

Example 3

7 - hydroxy - cholesterol - 3 - monobenzoate is heated with "Tetralin" for three hours at 200° C. under nitrogen. The reaction product contains 5% 7-dehydro-cholesterol-benzoate.

Example 4

On heating 2 parts of 7-hydroxy-cholesterol-3-monobenzoate with 25 parts of terpineol for three hours at 200° C. under nitrogen, a 31% yield of 7-dehydro-cholesterol-benzoate is obtained.

Example 5

An agitated mixture of 2 parts of 7-hydroxy-cholesterol-3-monobenzoate, 2 parts of anhydrous copper sulfate and 40 parts of toluene is refluxed for three hours. The cooled solution is decanted from the copper sulfate and the solvent distilled under reduced pressure. By crystallizing the residue from acetone, 7-dehydro-cholesterol-benzoate is obtained in an 88% yield of theory.

Example 6

An agitated mixture of 3 parts of 7-hydroxy-cholesterol-3-monobenzoate, 3 parts of fused potassium hydrogen sulfate and 45 parts of toluene is heated at reflux for two hours. The reaction mixture is filtered from the potassium hydrogen sulfate, is taken up in ether, is washed with water and is dried over sodium sulfate. The ether and toluene is distilled, the latter under reduced pressure, and 7-dehydro-cholesterol-benzoate is obtained in a 55% yield from the residue in the usual manner.

Example 7

A mixture of 2 parts of 7-hydroxy-cholesterol-3-monobenzoate, 2 parts of aluminum oxide and 45 parts of dried xylene is heated in a pressure bomb for three hours at 200° C. after which time 57% of 7-dehydro-cholesterol-benzoate is formed which can be isolated according to the known methods.

Example 8

On substituting toluene for xylene in the above reaction a 49% yield of 7-dehydro-cholesterol-benzoate is obtained along with a 30% recovery of starting material by concentration of the acetone mother liquor.

Example 9

When cyclohexane is substituted for xylene or toluene in the above reactions, 7-dehydro-cholesterol-benzoate is isolated in a 42% yield along with a 50% recovery of starting material.

Example 10

An agitated mixture of 5 parts of 7-hydroxy-cholesterol-3-monobenzoate, 5 parts of aluminum oxide and 25 parts of dimethyl aniline is heated under nitrogen for two hours at 196° C. On cooling, the Al_2O_3 is filtered off, rinsed with ether and the filtrate is distilled under reduced pressure to remove the dimethyl anilne. The residue is taken up in acetone. On cooling, 7-dehydro-cholesterol-benzoate is isolated in a 4% yield and an 80% recovery of starting material is obtained from the filtrate.

Example 11

A mixture of 3.4 parts of 7-hydroxy-cholesterol-3-monobenzoate and 3.4 parts of anhydrous aluminum oxide is heated under nitrogen for one hour at 200° C. On cooling, the mixture is extracted four times with 20-part portions of ether. The ether layer is washed twice with 10% sodium hydroxide and then with water until neutral to litmus. After evaporation of the ether, 7-dehydro-cholesterol-benzoate is obtained in 45% yield in the usual way.

Example 12

On heating the above mixture for 1.5 hours at 200° C., a 37.5% yield of 7-dehydro-cholesterol-benzoate is obtained.

Example 13

An agitated mixture of 2 parts of 7-hydroxy-cholesterol-3-monobenzoate, 2 parts of calcium carbide and 45 parts of "Tetralin" is refluxed under nitrogen for two hours. The reaction product is then extracted from CaC_2 with ether. After distilling ether and "Tetralin," the latter under reduced pressure, the residue is taken up in acetone. On cooling, a 47% yield of 7-dehydro-cholesterol-benzoate is obtained. A 50% recovery of starting material is isolated from the filtrate.

Example 14

Equal parts by weight of 7-hydroxy-cholesterol-3-monobenzoate and calcium carbide are heated under nitrogen for two hours at 200° C. After cooling, the mixture is extracted with ether and the ether extract is dried over sodium sulfate. After evaporation of the ether, a 21% yield of 7-dehydro-cholesterol-benzoate is isolated from the residue in the usual way. A 75% recovery of starting material is obtained from the filtrate.

Example 15

Two parts of 7-hydroxy-cholesterol-3-monobenzoate is dissolved in 30 parts of glacial acetic acid and the solution is heated with agitation at 60° C. for two hours. The solution is cooled, is diluted with water and is extracted with ether. After drying, the ether and acetic acid are distilled, the latter under reduced pressure. A 26% yield of 7-dehydro-cholesterol-3-benzoate is obtained from the residue in the usual way.

Example 16

Two parts of p-toluene-sulfone chloride dissolved in 25 parts of benzene is added to an agitated solution of two parts of 7-hydroxy-cholesterol-3-monobenzoate dissolved in 25 parts of benzene. The mixture is warmed to 45–50° C. and is held at that temperature for ten minutes. After cooling to room temperature, the mixture is extracted with ether. The ether extract is washed twice with 10% hydrochloric acid, then with water until neutral to litmus, twice with 10% sodium hydroxide and with water until neutral to litmus. After evaporation of the dried ether, 7-dehydro-cholesterol-3-benzoate is isolated in a 36% yield from the residue in the normal way.

Example 17

Ten parts of 7-hydroxy-cholesterol-3-monobenzoate is dissolved in 150 parts of pyridine and 11.4 parts of p-toluene sulfone chloride is added portionwise. After allowing this mixture to stand overnight, the solution is diluted with water and is extracted with ether. The ether extract is treated as described in the example above. After saponification of the residue with alcoholic-caustic, 7-dehydro-cholesterol is obtained in a 8–10% yield as determined by a spectrographic analysis.

Example 18

Two parts of ethyl sulfone chloride is added dropwise to an agitated solution of 2 parts of 7-hydroxy-cholesterol-3-monobenzoate dissolved in 20 parts of dried pyridine and the mixture agitated for 16 hours. After this treatment, a 21% yield of 7-dehydro-cholesterol-3-benzoate is obtained by the method described in Example 16.

It is to be understood that the foregoing examples are illustrative merely of a few of the many embodiments of this invention. They may be varied widely with respect to the individual reactants, the amounts thereof and the conditions of reaction without departing from the scope hereof.

In place of 7-hydroxy-cholesterol-3-mono-benzoate it is to be understood that other 7-hydroxy-sterol-3-monoesters or mixtures thereof may be employed. These sterols should advisably have a double bond in a position adjacent to the 7-hydroxy group and should possess a sterol side chain. In general, the invention is applicable to those compounds having a cyclo-pentano-per-hydro-phenanthrene skeleton, a sterol side chain, a 7-hydroxy group, and a double bond in the 5,6-position. Among the compounds coming within this category are, for example, 7-hydroxy-cholesterol, 7-hydroxy-sitosterol, and 7-hydroxy-stigmasterol.

In place of the 3-monobenzoate referred to in the examples it is to be understood that other monoesters produced from either mono- or poly-carboxylic acids may be utilized. A few of the many compounds included within this class are esters obtained from acids such as acetic, propionic, oxalic, succinic, adipic, 3,5-dinitrobenzoate, p-nitrobenzoate, 3-nitrophthalic, 4-chlorophthalic, 4-methoxy-phthalic, etc. It is also contemplated that the 3-position in the sterol skeleton may have an ether or a halogen group substituted thereon in place of the previously mentioned ester group. A few groups of this type are, in the case of ethers, methyl, ethyl, aryl, etc., and in the case of halogens, chloro, bromo, etc.

Dehydration of the compounds referred to previously and those related thereto or suggested thereby is accomplished, as a general rule, at elevated temperatures and preferably in the presence of suitable dehydrating agents. The reaction may be carried out in either the liquid or the solid phase. As mentioned previously, the liquid phase would involve the presence of suitable liquid dehydrating agents, such as, for example, hydrocarbons, alcohols, amines and the like, with or without additional dehydrating agents or mixtures thereof. The solid phase would comprise the presence of solid dehydrating agents, such as metal oxides, metal salts, metallic carbides, alkyl and acyl sulfone chlorides, and the like, including mixtures of the same and related dehydrating agents.

It is to be understood that the particular dehydrating agent or agents selected should not destroy the resulting 7-dehydro-sterol compound. In order to determine whether any given dehydrating agent is suitable for this purpose the following simple test may be applied thereto. Two mg. of ergosterol or a similar provitamin may be heated in the presence of the dehydrating agent to 100° C. for one-half hour. Heating is preferably conducted in a sealed tube containing an inert medium such as nitrogen, or the tube may be evacuated before sealing. The reaction product is then diluted with 100 cc. of ethyl alcohol and spectroscopically examined for the presence of ergosterol. (See "Chemistry and Physiology of Vitamins," Rosenberg, page 350.) If the ergosterol has remained unchanged, the dehydrating agent is suitable. On the other hand, if the ergosterol is altered or destroyed the compound is not generally satisfactory.

Dehydration products of 7-hydroxy-sterols produced as aforesaid may then be treated in the customary manner to remove therefrom the 3-substituent. For instance, when 7-hydroxy-cholesterol-3-monobenzoate is dehydrated to produce 7-dehydro-cholesterol-3-monobenzoate, this latter product is saponified with caustic alkali or alkaline-earth metal hydroxides in the presence of a suitable solvent such as alcohol. The resulting product is the desired 7-dehydro-cholesterol.

In accordance with the present invention, a new and simplified process for the production of desirable 7-dehydro-sterols has been discovered. This process eliminates one of the steps formerly thought to be essential for the manufacture of these compounds. By eliminating this step the process is appreciably simplified and rendered considerably more economical. In carrying out this reaction a wide variety of dehydrating agents suitable for this purpose may be used. Excellent yields of the desired products are obtained and the reaction has been found to proceed smoothly and efficiently.

As many widely different embodiments of this invention may be made without departing from the spirit and scope thereof, it is to be understood that the invention is not limited to the specific embodiments thereof except as defined in the appended claims.

We claim:

1. A process for dehydrating 7-hydroxy-cholesterols which comprises heating a 3-monoester of 7-hydroxy-cholesterol in the presence of a solid dehydrating agent selected from the class consisting of anhydrous copper sulfate, fused potassium hydrogen sulfate, aluminum oxide, and calcium carbide.

2. A process for dehydrating 7-hydroxy-cholesterols which comprises heating the 3-monobenzoate of 7-hydroxy-cholesterol in the presence of a solid dehydrating agent selected from the class consisting of anhydrous copper sulfate, fused potassium hydrogen sulfate, aluminum oxide, and calcium carbide.

3. A process for dehydrating 7-hydroxy-cholesterol-3-monobenzoate which comprises heating said compound in the presence of anhydrous copper sulfate.

4. A process for dehydrating 7-hydroxy-cholesterol-3-monobenzoate which comprises refluxing said compound and toluene in the presence of anhydrous copper sulfate.

WALTER C. MEULY.
HANS R. ROSENBERG.
DANIEL H. TERRY.