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2,755,289

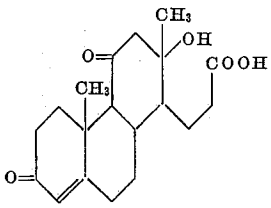
ANHYDRO DERIVATIVES OF 2,4b-DIMETHYL-2-HYDROXY-4,7-DIOXO - 1,2,3,4,4a,4b,5,6,7,9,10,10a-DODECAHYDROPHENANTHRENE - 1 - PROPIONIC ACID

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3 Claims. (Cl. 260—343.2)

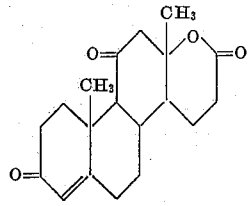
The present invention is concerned with a new group of compounds which can be regarded as dehydration products of 2,4b-dimethyl-2-hydroxy-4,7-dioxo-1,2,3,4,-4a,4b,5,6,7,9,10,10a - dodecahydrophenanthrene-1-propionic acid of the following structural formula



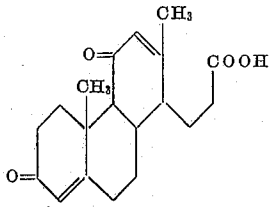
The dehydration products, or anhydro derivatives, have the empirical formula

$C_{19}H_{24}O_4$

and the structural formulas



and



accordingly as the 2-hydroxyl group can be regarded as participating in a dehydration reaction with the carboxylic acid group to yield a lactone, or with the adjacent methylene group to yield an unsaturated carboxylic acid.

This application is a continuation-in-part of my copending application Serial No. 428,382, filed May 7, 1954.

The relationship between the two aforementioned dehydration products is that of an unsaturated carboxylic acid and the corresponding isomeric lactone. In many such instances the lactone is by far the more stable isomer and is preferentially formed by isomerization of the corresponding unsaturated carboxylic acid with dilute mineral acid. In the case of the compounds of the present invention, however, the unsaturated carboxylic acid is made relatively more stable by virtue of participation of the double bond in an α,β-unsaturated ketone system. The compounds of this invention can exist either as essentially pure compounds or as an isomeric mixture. Satisfactory methods have been provided for accomplishing each of these results.

In a preferred method for the manufacture of the lactonic isomer, 2,4b-dimethyl-2-hydroxy-4,7-dioxo-1,2,3,-4,4a,4b,5,6,7,9,10,10a-dodecahydrophenanthrene - 1 - propionic acid lactone, otherwise known as 17a-oxa-D-homo-4-androstene-3,11,17-trione, an 11-hydroxy-17a-oxa-D-homo-4-androstene-3,17-dione is subjected to a carefully controlled oxidation with chromium trioxide. Both isomeric products are formed in this reaction, but if the entire process is carried out at or below room temperature, the lactone predominates in the crude product and is obtained in a pure form by recrystallization. However, if the solution containing chromium salts and acetic acid is heated and concentrated to dryness at an elevated temperature (after the addition of sodium sulfite solution to reduce the excess chromium trioxide) formation of the unsaturated carboxylic acid is promoted, and under these circumstances it is possible to isolate the pure unsaturated acid by recrystallization of the crude reaction product. However, a preferred method of manufacture for the unsaturated carboxylic acid is by isomerization of the lactone.

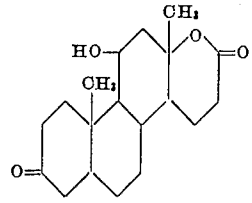
When 2,4b-dimethyl - 2 - hydroxy-4,7-dioxo-1,2,3,4,4a,-4b,5,6,7,9,10,10a - octahydrophenanthrene - 1 - propionic acid lactone is treated with a base, such as by stirring it with dilute aqueous sodium hydroxide solution, it enters into solution as the sodium salt of the hydroxy acid formed by the addition of the elements of water to the lactone ring. In carrying out this process it is preferred to dissolve the lactone in warm ethanolic solution, cool to room temperature, add the aqueous base, and concentrate the solution at or below room temperature until the ethanol is substantially removed. In this manner attack of the basic reagent on the other sensitive groups is minimized. When the resulting aqueous solution containing the sodium salt of 2,4b-dimethyl-2-hydroxy-4,7-dioxo - 1,2,3,4,4a,4b,5,6,7,9,10,10a - dodecahydrophenanthrene-1-propionic acid is acidified a variety of products can form, depending on the conditions. At low temperature, in the absence of an excess of mineral acid, the organic hydroxy acid, 2,4b-dimethyl-2-hydroxy-4,7-dioxo-1,2,3,4,4a,4b,5,6,7,9,10,10a - dodecahydrophenanthrene-1-propionic acid is formed. However, this acid is relatively unstable, and in the presence of an excess of mineral acid, or at an elevated temperature, it is converted to one or to a mixture of its dehydration products. The unsaturated carboxylic acid isomer, 2,4b-dimethyl-4,7-dioxo-1,-4,4a,4b,5,6,7,9,10,10a - decahydrophenanthrene -1- propionic acid is obtained in a good yield and in an almost pure form when the acidification is conducted by adding the aqueous solution of the sodium salt to an excess of hydrochloric acid maintained at about 50–60° C. When the acidification is conducted by adding an excess of cold dilute hydrochloric acid all at once to a cold solution of the sodium salt, a mixed reaction product results. This can be separated into the lactonic and non-lactonic components by taking advantage of the different rates of solubility in cold dilute sodium hydroxide solution. When the solid reaction product is stirred for a very short period of time in cold dilute sodium hydroxide solution, the lactone dehydration product remains insoluble and can be recovered by filtration. The carboxylic acid, on the other hand, dissolves almost immediately in the dilute sodium hydroxide solution and can be recovered by reprecipitation with hydrochloric acid.

The compounds of this invention possess valuable pharmaceutical and especially cardiovascular, anti-inflammatory and hormonal properties. They are potent hypotensive agents, and are also valuable in the treatment of such conditions as allergic arteritis. These compounds are also useful as intermediates in the chemical synthesis of other medicinally valuable compounds.

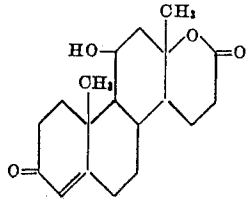
The following examples illustrate in detail some of the preferred methods of practicing the invention. However, it is not to be construed as limited thereby in spirit or in scope since it will be obvious to those skilled in the art that numerous modifications in materials and methods can be practiced without departing from the invention. In these examples, temperatures are given in degrees centigrade (° C.) and amounts of materials as parts by weight.

Example 1

A solution of 1 part of 17a-oxa-D-homo-4-androstene-3,17-dione (2,4b-dimethyl-2-hydroxy-7-oxo-1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydrophenanthrene-1-propionic acid lactone, testololactone) in 5000 parts of citrated bovine blood and 5000 parts of citrated calcium-free Tyrode solution containing 50 parts of glucose is perfused 7 times through bovine adrenal glands lacerated at the surface at a temperature of 36.5 to 37.6° C. in the course of 3 hours. The perfusate is then extracted with isopropyl acetate. The extract is washed with water, dried by azeotropic distillation and concentrated at reduced pressure in a nitrogen atmosphere to a residue of about 50 parts. The residue is diluted with 900 parts of benzene and poured onto a chromatography column containing 100 parts of silica gel. The column is washed with 500 parts of a 10% and 3000 parts of a 20% solution of ethyl acetate in benzene to remove unreacted testololactone and impurities. Elution with a 25% solution of ethyl acetate in benzene yields first eluates which, on concentration and recrystallization of the residue from ethyl acetate, yield needles melting at about 267–270° C. The ultraviolet absorption spectrum of this product shows little absorption in the region of 240 millimicrons. This compound is 11β-hydroxy-17a-oxa-D-homoandrostane - 3,17 - dione having the following structural formula



Further elution of the chromatography column with a 25% solution of ethyl acetate in benzene yields the principal product of the adrenal perfusion. This product, obtained by concentration of the eluates and recrystallization, crystallizes from ethyl acetate or from acetone in colorless, thick, dense rhombohedra melting at about 264–267° C. On crystallization from ethanol or mixtures of ethanol and ethyl acetate, the product is obtained in cottony needles. The specific rotation of a 0.9% acetone solution is +41°. The ultraviolet spectrum of a methanolic solution shows an absorption maximum at 240 millimicrons with a molecular extinction coefficient of 16,700. Principal infrared absorption maxima in chloroform are observed at about 5.84, 6.03, 6.19, 6.92, 7.82, and 9.09 microns. In a potassium bromide disc, a strong absorption maximum attributable to the hydroxyl group appears at about 2.9 microns. This product gives an intense green fluorescence with concentrated sulfuric acid, becoming apparent only after a contact time of several minutes. This compound is 11β-hydroxy-17a-oxa-D-homo-4-androstene-3,17-dione having the following structural formula



Example 2

Two parts of 11β-hydroxy-17a-oxa-D-homo-4-androstene-3,17-dione (2,4b-dimethyl-2,4-dihydroxy-7-oxo-1,2,3,4,4a,4b,5,6,7,9,10,10a - dodecahydrophenanthrene - 1-propionic acid-δ-lactone) is dissolved in 70 parts of glacial acetic acid by prolonged shaking at room temperature. To this solution is added a solution of 3 parts of chromium trioxide, 5 parts of water and 20 parts of glacial acetic acid. The mixture is quickly cooled to about 12° C. and maintained at that temperature for 2 hours. It is then permitted to warm to 20° C. in the course of a half hour. The oxidation mixture is then treated with a solution of 9 parts of sodium sulfite in 150 parts of water and evaporated at room temperature. The slightly wet residue is stirred with 80 parts of water until no more of the solid enters into solution. The suspension is maintained at 0° C. for 3 hours. The solid product is collected on a filter, washed well with water, air-dried and recrystallized twice from ethyl acetate. Thus, thick, white needles or rods are obtained which melt at about 238–241° C. The ultraviolet spectrum of a methanolic solution shows an absorption maximum at about 238 millimicrons with a molecular extinction coefficient of 17,000. Principal infrared absorption maxima in chloroform appear at about 5.80, 6.02, 6.18, 6.90, 7.24, 7.42, 8.02, 8.64, and 9.05 microns. The specific rotation of a 1% acetone solution is +92.5°. This compound is 2,4b-dimethyl-2-hydroxy-4,7-dioxo - 1,2,3,4,4a,4b,5,6,7,9,10,10a - dodecahydrophenanthrene-1-propionic acid lactone.

The isomeric compound, 2,4b-dimethyl-4,7-dioxo-1,4,4a,4b,5,6,7,9,10,10a - decahydrophenanthrene - 1 - propionic acid, can become a predominant product of the oxidation reaction under experimental conditions described hereinafter.

Example 3

A solution prepared by heating 1 part of 2,4b-dimethyl-2-hydroxy-4,7-dioxo - 1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydrophenanthrene-1-propionic acid lactone with 160 parts of ethanol is cooled to room temperature and treated by the addition of 2 parts of sodium hydroxide in 50 parts of water. This solution is allowed to stand at room temperature for 15 minutes and is then concentrated in a nitrogen atmosphere, at or below room temperature, to about one-fifth of its original volume. It is desirable to carry out this concentration fairly rapidly, for example over a period of up to 2 hours. The remaining solution is added gradually, with stirring, to a solution prepared from 20 parts of concentrated hydrochloric acid and 100 parts of water, maintained at about 50–60° C. during the addition of the basic solution. A precipitate does not form immediately, but soon the mixture becomes turbid and finally a crystalline precipitate separates. This crude product is collected on a filter and washed with water. A sample of this material redissolves immediately in cold dilute sodium hydroxide solution, demonstrating that it is almost entirely the unsaturated carboxylic acid isomer, rather than the lactone which requires a longer contact time for re-solution in base. Purification of the crude product by recrystallization from a mixture of ethyl acetate and petroleum ether affords 2,4b-dimethyl-4,7-dioxo-1,4,4a,4b5,6,7,9,10,10a-decahydrophenanthrene- 1 - propionic acid melting at 166–168° C. This compound has a specific rotation of +131° in chloroform solution. It has an ultraviolet absorption maximum at about 237 millimicrons with a molecular extinction coefficient of 27,400. Prominent infrared absorption maxima in chloroform solution are observed at 5.85, 6.02 (broad, with shoulder at 6.18), 6.98, 7.26, 7.64, 7.84, 8.38, and 8.80 microns.

Example 4

A solution prepared by heating 1 part of 2,4b-dimethyl-2-hydroxy-4,7-dioxo-1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydrophenanthrene-1-propionic acid lactone with 160 parts

of ethanol is cooled to room temperature and treated by the addition of 2 parts of sodium hydroxide in 50 parts of water. This solution is allowed to stand at room temperature for 15 minutes and is then concentrated in a nitrogen atmosphere at or below room temperature, to about one-fifth of its original volume. It is desirable to carry out this concentration fairly rapidly, for example over a period of up to 2 hours. The residual solution is diluted with 100 parts of water and (at room temperature) 20 parts of concentrated hydrochloric acid is added all at once. The mixture starts to become turbid immediately and soon an insoluble product begins to separate. The suspension is refrigerated for about 4 hours to insure complete separation of the crude reaction product, which is partly crystalline and partly gummy. The crude product consists primarily of the unsaturated carboxylic acid isomer, as filtration affords crystals which melt at about 160° C. and which yield pure 2,4b-dimethyl-4,7 - dioxo - 1,4,4a,4b,5,6,7,9,10,10a - decahydrophenan - threne-1-propionic acid by recrystallization from a mixture of ethyl acetate and petroleum ether. The smaller amount of lactonic component which is present in the crude product can be isolated by stirring the entire precipitated reaction product with cold dilute sodium hydroxide solution for about one minute and collecting on a filter the fraction which does not dissolve during that period of time.

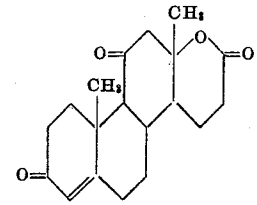
Example 5

A solution of 11β-hydroxy-17a-oxa-D-homo-4-androstene-3,17-dione (2,4b-dimethyl-2,4-dihydroxy-7-oxo-1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydrophenanthrene - 1-propionic acid-δ-lactone) is prepared by stirring 12 parts of this compound with 410 parts of glacial acetic acid at about 35° C. and cooling the solution to room temperature. There is then added over a 2 minute period a solution prepared from 18 parts of chromium trioxide, 30 parts of water and 125 parts of glacial acetic acid. The reaction mixture is cooled to about 10° C. and maintained at this temperature for approximately 2 hours. Over a period of a half hour it is then allowed to warm to about 20° C. and then poured, with stirring, into a solution of 54 parts of sodium sulfite and 900 parts of water. The resulting solution is evaporated completely to dryness on a steam bath. The solid residue is stirred for 1 hour with 480 parts of water and the mixture is refrigerated for 5 hours. The insoluble gummy product is washed several times by decantation with water and redissolved in glacial acetic acid. The acetic acid solution is stirred into several times its volume of water and the dark, gummy precipitate is washed by decantation with water, air-dried, and extracted with warm ethyl acetate. The ethyl acetate solution is filtered from some darkly-colored, insoluble material which is discarded. When the pale yellow filtrate is concentrated to a small volume, diluted with hot petroleum ether and cooled, there is formed a crystallizate of 2,4b-dimethyl-4,7-dioxo-1,4,4a,-4b,5,6,7,9,10,10a - decahydrophenanthrene - 1 - propionic acid, identical with the product of Example 3.

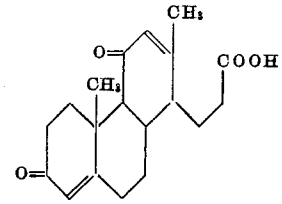
What is claimed is:

1. A monoanhydro-2,4b-dimethyl-2-hydroxy-4,7-dioxo-1,2,3,4,4a,4b,5,6,7,9,10,10a-dodecahydrophenanthrene-1 - propionic acid having the empirical formula $C_{19}H_{24}O_4$.

2. A compound having the structural formula



3. A compound having the structural formula



References Cited in the file of this patent

Levy et al.: J. Biol. Chem., vol. 171, pp. 71–79 (1947).