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PROCESS FOR PRODUCING $\Delta^{9,11}$-12-KETO STEROIDS FROM $\Delta^{8,9}$-12-KETO STEROIDS

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18 Claims. (Cl. 260—397.1)

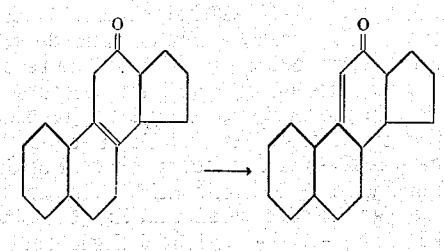
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This invention relates to compounds of the cyclopentanopolyhydrophenanthrene series having a 12-keto group and a double bond in the 9,11 position, and more particularly to the preparation of such compounds.

The cyclopentanopolyhydrophenanthrene compounds having a 12-keto group and a double bond in the 9,11 position are useful as intermediates in the preparation of steroid compounds having an 11-keto group. For example, 3-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid can be utilized as a starting material to prepare 3-hydroxy-11-ketocholanic acid and derivatives thereof which may be further treated to obtain the therapeutically important compound, Kendall's Compound E (17-hydroxy-11-dehydrocorticosterone).

It is an object of the present invention to provide an improved process for preparing $\Delta^{9,11}$-12-keto cyclopentanopolyhydrophenanthrene compounds. It is a further object to provide a process for converting cyclopentanopolyhydrophenanthrene compounds having a 12-keto substituent and a double bond in the 8,9 position to the desired $\Delta^{9,11}$-12-keto compounds. Another object is to provide an improved method for obtaining 3-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid. Other objects of this invention will be apparent from the detailed disclosure hereinafter provided.

In accordance with one embodiment of our invention, we have found that cyclopentanopolyhydrophenanthrene compounds having a 12-keto substituent and a double bond in the 8,9 position are readily converted to the corresponding $\Delta^{9,11}$-12-keto compound by reaction with a mineral acid or a strong alkali. This reaction may be illustrated as follows:



The compounds illustrated above may also contain substituents such as hydroxy, acyloxy, keto, alkyl, carboxyalkyl, and the like in rings A, B and D.

The reaction is effected by intimately contacting the $\Delta^{8,9}$-12-keto compound with a mineral acid or a strong alkali. Mineral acids suitable

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for this purpose include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and the like. By the term, strong alkalis, as used herein, is meant those alkaline substances which in solution exhibit a pH above 8, such as the alkali metal hydroxides and alkali metal alcoholates (inter alia, sodium hydroxide, potassium hydroxide, sodium methoxide, sodium ethoxide, potassium methoxide, and the like). After the isomerization is completed, the desired product is conveniently recovered in accordance with conventional methods.

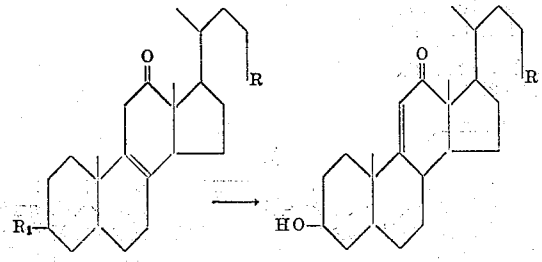
As suitable starting materials in the process of our invention there may be mentioned, $\Delta^{8,9}$-12-ketopregnene, 3-hydroxy-$\Delta^{8,9}$-12-ketopregnene, 3-acyloxy-$\Delta^{8,9}$-12-ketopregnene, $\Delta^{8,9}$-12-ketocholenic acid, 3-hydroxy-$\Delta^{8,9}$-12-ketocholenic acid, 3-acyloxy-$\Delta^{8,9}$-12-ketocholenic acid, $\Delta^{8,9}$-12-ketoetiocholenic acid, 3-hydroxy-$\Delta^{8,9}$-12-ketoetiocholenic acid, 3-acyloxy-$\Delta^{8,9}$-12-ketoetiocholenic acid, esters of such acids, and the like. When the starting compound contains an acyloxy substituent this group is hydrolyzed under the reaction conditions to yield a hydroxy substituent. Also, when esters are treated with strong alkalies, hydrolysis occurs and the free acid derivative is obtained. However, this is immaterial to our invention since, if desired, the isomerized product may be acylated or esterified in accordance with conventional chemical practice to obtain the desired acylated and/or esterified derivative.

In carrying out the process of our invention we have achieved maximum yields of the desired product under optimum conditions by reacting the $\Delta^{8,9}$-12-keto cyclopentanopolyhydrophenanthrene compound with the mineral acid or strong alkali is a suitable solvent medium. We have found that lower aliphatic alcohols (inter alia methyl alcohol, ethyl alcohol, isopropyl alcohol) or water-lower aliphatic alcohol mixtures, are particularly suitable as reaction mediums for our process.

In practice, we find that although the temperature can be varied somewhat depending upon the particular compound being isomerized, generally maximum yields are achieved by carrying out the reaction of the $\Delta^{8,9}$-12-keto compound with a strong alkali or a mineral acid at room temperatures.

The process of our invention is particularly valuable for converting $\Delta^{8,9}$-12-ketocholenic acids to the corresponding $\Delta^{9,11}$-12-ketocholenic acids. Thus, we have found it to be most useful for preparing 3-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid and esters thereof from the corresponding 3-hydroxy-

$\Delta^{8,9}$-12-ketocholenic acid or esters thereof. (As indicated previously, 3-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid is valuable as an intermediate in the preparation of Kendall's Compound E.) Alternatively, we may also use the corresponding 3-acyloxy compounds, for example the 3-acyloxy acids or 3-acyloxy ester, as starting materials for this purpose. In this case, as mentioned previously, the 3-acyloxy group is hydrolyzed under the reaction conditions to yield the isomerized product having a 3-hydroxy substituent. These particular reactions may be illustrated as follows:



wherein R represents a carboxy group or an esterified carboxy group convertible to carboxy by hydrolysis and R_1 represents a hydroxy or an acyloxy substituent convertible to hydroxy by hydrolysis.

In carrying out the isomerization of a 3-hydroxy-$\Delta^{8,9}$-12-ketocholenic acid to obtain the isomerized product having a double bond in the 9,11 position, we prefer to use a lower alkyl ester of the $\Delta^{8,9}$-compound as the starting material. In effecting the reaction with this starting material under our preferred conditions, the starting compound is dissolved in a lower aliphatic alcohol, the mineral acid or strong alkali added thereto, and the resulting reaction mixture permitted to stand at room temperature until the isomerization is completed. In this case, the course of the reaction, i. e. the shifting of the double bond from the 8,9 to the 9,11 position is conveniently followed by measuring the ultra-violet absorption spectrum of the solution. Since the $\Delta^{9,11}$ compounds produced exhibit a characteristic absorption spectrum due to the presence of a conjugated double bond system with chromophoric properties, whereas the starting compounds do not have an ultra-violet absorption spectrum, the course of the reaction is readily and conveniently followed by measuring the absorption spectrum. Generally, we find that it is preferable, when utilizing cholenic acids or derivatives thereof as the starting material in our process, not to permit the reaction mixture to stand longer than 40 hours, since some decomposition of the product appears to take place after that time.

It is indeed surprising to find that isomerization of $\Delta^{8,9}$-12-keto cyclopentanopolyhydrophenanthrene compounds can be effected to yield the corresponding $\Delta^{9,11}$-compounds. While the shifting of double bonds in steroids under hydrogenation conditions or with hydrochloric acid and acetic acid has been reported in the apocholic acid series, the isomerization of $\Delta^{8,9}$ steroids had not been reported previously. In the apocholic acid series, the migration of 7,8 or 14,15 double bonds to the more stable 8,14 position occurs, and it is therefore indeed unexpected to find that the 8,9-double bond will shift to the 9,11-position.

The preparation of the starting material, 3-acetoxy-$\Delta^{8,9}$-12-ketocholenic acid and the methyl ester thereof from cholic acid are described in the Journal of the Japanese Biochemical Society, volume 20, pages 144–147 (1948). The 3-hydroxy-$\Delta^{8,9}$-12-ketocholenic acid is readily obtained by hydrolyzing the corresponding 3-acetoxy compound in accordance with methods known in the art.

The following examples are presented to illustrate specific embodiments of our invention:

Example 1

2 g. of 3(α)-acetoxy-$\Delta^{8,9}$-12-ketocholenic acid was dissolved under nitrogen in 30 cc. of 0.6 N methanolic hydrogen chloride. The resulting solution quickly became pale yellow and all of the solid dissolved in one-half hour. The solution was then maintained at room temperature for forty hours and finally concentrated to dryness in vacuo. Water was added to the resulting residue; and the off-white solid was removed by filtration, washed with an aqueous sodium bicarbonate solution, then with water, and finally dried. After recrystallization from aqueous methanol the methyl-3(α)-hydroxy-$\Delta^{9,11}$-12-ketocholenate was found to melt at 115–118° C. and did not depress the melting point of authentic methyl-3(α)-hydroxy-$\Delta^{9,11}$-12-ketocholenate. The product was found to have a specific rotation: $[\alpha]_D^{22}=+104°$ (1% in chloroform).

The crude methyl-3(α)-hydroxy-$\Delta^{9,11}$-12-ketocholenate prepared above was dissolved in 15 cc. of methanol and stirred while 0.38 g. of sodium hydroxide in 1 cc. of water was added dropwise. The alkali was washed in with 1 cc. of water, and the solution was warmed at 40–42° for 45 minutes. The yellow solution was diluted with 15 cc. of water and concentrated to a mush in vacuo. Water (15 cc.) and acetone (6 cc.) were added to the residue, and the solution was cooled to room temperature. The solution was stirred and acidified to litmus with 1.1 cc. of glacial acetic acid added dropwise. The mixture was diluted with 40 cc. of water and chilled for one hour. The solid was filtered, washed with water and recrystallized twice from aqueous methanol. The 3(α)-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid so obtained was found to melt at 173–175° C. and had a specific rotation of $[\alpha]_D^{22}=+103°$ (1% in chloroform). The product had an ultra-violet absorption spectrum, λ maximum 2400 Å.: E% 287, E_M% 11,200. This material did not depress the melting point of an authentic sample (M. P. 176–177.5°) of 3(α)-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid.

Example 2

1 g. of 3-acetoxy-$\Delta^{8,9}$-12-ketocholenic acid was suspended in 20 cc. of methanol and 20 cc. of 30% sodium hydroxide was added. The reaction mixture was cooled to room temperature and kept standing overnight. The dark green solution was concentrated to a slush in vacuo. The residue was dissolved in hot water and acidified to litmus with 36% acetic acid. The acidified mixture was cooled, filtered, and the precipitated 3(α)-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid was washed with water. The $\Delta^{9,11}$-acid so obtained was recrystallized from aqueous methanol. The 0.7 g. of product so obtained was found to melt at 174–177° C. and a 1% chloroform solution had a rotation, $[\alpha]_D^{23}=+100°$. The ultra-violet absorption spectrum exhibited a maximum, λ at 2400 Å. with E% of 280. A mixed melting point

with an authentic sample of 3(α)-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid gave no depression.

Example 3

0.0126 g. of methyl 3-acetoxy-$\Delta^{8,9}$-12-ketocholenate was dissolved in 1 cc. methanolic HCl (0.6 molar HCl) and the solution was allowed to stand at room temperature. Formation of methyl 3-hydroxy-$\Delta^{9,11}$-12-ketocholenate was measured by appearance of the ultra-violet adsorption spectrum; after 7½ hours, Λ max., 2400 Å., E% 252.

Example 4

0.335 g. of 3-hydroxy-$\Delta^{8,9}$-12-ketocholenic acid was dissolved in 5 cc. methanolic HCl (0.6 molar HCl), and the solution was allowed to stand at room temperature. Formation of the $\Delta^{9,11}$-compound was recognized by measurement of the ultra-violet absorption spectrum; after 13 hours, Λ max. 2400 Å., E% 213.

Example 5

0.0168 g. of 3-hydroxy-$\Delta^{8,9}$-12-ketocholenic acid was dissolved in 1 cc. of methanolic sodium hydroxide (2.5 cc. methanol+2.5 cc. 30% aqueous NaOH). The solution was allowed to stand at room temperature, and the formation of the 3-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid was determined by measurement of the ultra-violet absorption spectrum of the solution:

After 13 hours, Λ max. 2400 Å.—E% 171
After 20 hours, Δ max. 2400 Å.—E% 200
After 37 hours, Λ, max. 2400 Å.—E% 279

Various changes and modifications may be made in carrying out the present invention without departing from the spirit and scope thereof. Insofar as these changes and modifications are within the purview of the annexed claims, they are to be considered as part of our invention.

We claim:

1. The process for preparing a $\Delta^{9,11}$-12-keto compound of the cyclopentanopolyhydrophenanthrene series which comprises reacting a $\Delta^{8,9}$-12-keto cyclopentanopolyhydrophenanthrene compound with a member selected from the group consisting of mineral acids and strong alkalis.

2. The process for preparing a $\Delta^{9,11}$-12-keto compound of the cyclopentanopolyhydrophenanthrene series which comprises reacting a $\Delta^{8,9}$-12-keto cyclopentanopolyhydrophenanthrene compound with a member selected from the group consisting of mineral acids and strong alkalis, and recovering the corresponding $\Delta^{9,11}$-12-keto cyclopentanopolyhydrophenanthrene compound from the resutling reaction mixture.

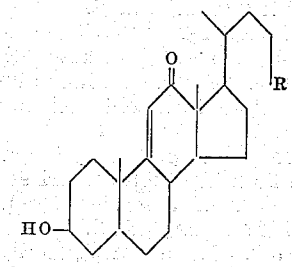
3. The process for preparing a $\Delta^{9,11}$-12-keto-compound of the cyclopentanopolyhydrophenanthrene series which comprises reacting a $\Delta^{8,9}$-12-keto cyclopentanopolyhydrophenanthrene compound with a mineral acid.

4. The process for preparing a $\Delta^{9,11}$-12-keto compound of the cyclopentanopolyhydrophenanthrene series which comprises reacting a $\Delta^{8,9}$-12-keto cyclopentanopolyhydrophenanthrene compound with a strong alkali.

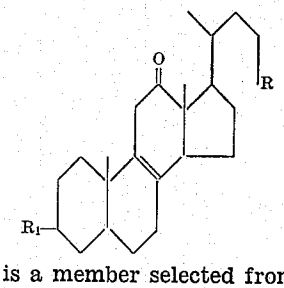
5. The process for preparing a $\Delta^{9,11}$-12-ketocholenic acid which comprises reacting a $\Delta^{8,9}$-12-ketocholenic acid with a mineral acid.

6. The process for preparing a $\Delta^{9,11}$-12-ketocholenic acid which comprises reacting a $\Delta^{8,9}$-12-ketocholenic acid with a strong alkali.

7. The process for preparing a compound of the formula:

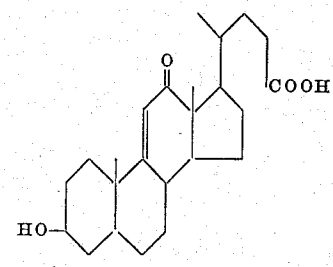


wherein R is a member selected from the group consisting of carboxy and esterified carboxy which comprises reacting a mineral acid with a compound of the formula:

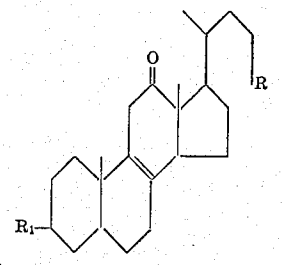


wherein R is a member selected from the group consisting of carboxy and esterified carboxy and R_1 is a member selected from the group consisting of hydroxy and acyloxy.

8. The process for preparing a compound of the formula:



which comprises reacting a strong alkali with a compound of the formula:



wherein R is a member selected from the group consisting of carboxy and esterified carboxy and R_1 is a member selected from the group consisting of hydroxy and acyloxy.

9. The process for preparing 3-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid which comprises reacting 3-hydroxy-$\Delta^{8,9}$-12-ketocholenic acid with a mineral acid.

10. The process for preparing 3-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid which comprises reacting 3-hydroxy-$\Delta^{8,9}$-12-ketocholenic acid with a strong alkali.

11. The process for preparing a lower alkyl ester of 3-hydroxy-$\Delta^{9,11}$-ketocholenic acid which comprises reacting a lower alkyl ester of 3-hydroxy-$\Delta^{8,9}$-12-ketocholenic acid with a mineral acid.

12. The process for preparing 3-hydroxy-$\Delta^{9,11}$-

ketocholenic acid which comprises reacting a lower alkyl ester of 3-hydroxy-$\Delta^{8,9}$-12-ketocholenic acid with a strong alkali.

13. The process for preparing a lower alkyl ester of 3-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid which comprises reacting a lower alkyl ester of 3-acyloxy-$\Delta^{8,9}$-12-ketocholenic acid with a mineral acid.

14. The process for preparing 3-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid which comprises reacting a lower alkyl ester of 3-acyloxy-$\Delta^{8,9}$-12-ketocholenic acid with a strong alkali.

15. The process for preparing methyl 3(α)-hydroxy-$\Delta^{9,11}$-12-ketocholenate which comprises reacting methyl 3(α) - hydroxy-$\Delta^{8,9}$-12-ketocholenate with a mineral acid.

16. The process for preparing 3(α)-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid which comprises reacting methyl 3(α) - hydroxy-$\Delta^{8,9}$-12-ketocholenate with a strong alkali.

17. The process for preparing methyl 3(α)-hydroxy-$\Delta^{9,11}$-12-ketocholenate which comprises reacting methyl 3(α) - acetoxy-12-ketocholenate with a mineral acid.

18. The process for preparing 3(α)-hydroxy-$\Delta^{9,11}$-12-ketocholenic acid which comprises reacting methyl 3(α) - acetoxy-12-ketocholenate with a strong alkali.

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No references cited.