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STEROID ALKALI-METAL ENOLATES

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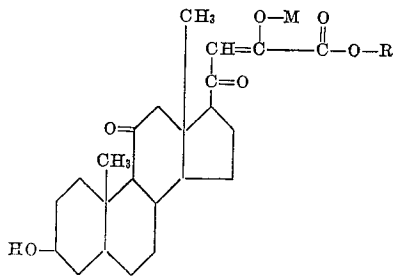
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17 Claims. (Cl. 260—397.1)

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The present invention relates to certain steroid metal enolates and is more particularly concerned with 21 - alkoxyoxalyl-3-hydroxypregnane-11,20-dione alkali-metal enolates and to a novel process for the production thereof.

The novel compounds of the present invention may be represented by the following structural formula:



wherein M is an alkali metal and R is alkyl and wherein the 3-hydroxy group has the alpha or beta stereoconfiguration.

The novel process of the present invention involves condensation of 3-hydroxypregnane-11,20-dione with an alkyl di-ester of oxalic acid in the presence of an alkali-metal base to produce a 21-alkoxyoxalyl - 3 - hydroxypregnane-11,20-dione alkali-metal enolate.

An object of the present invention is to provide novel 21-alkoxyoxalyl-3-hydroxypregnane-11,20-dione alkali-metal enolates. Another object of the present invention is the provision of a process for the production of 21-alkoxyoxalyl-3-hydroxypregnane - 11,20 - dione alkali-metal enolates. A further object of the present invention is the provision of a process for the production of 21-alkoxyoxalyl - 3 - hydroxypregnane-11,20-dione alkali-metal enolates without the concomitant formation of alkoxyoxalyl alkali-metal enolates at other positions of the molecule. Other objects of the present invention will be apparent to those skilled in the art to which this invention pertains.

The novel compounds of the present invention have utility as stable forms of the corresponding keto acids, keeping well, as convenient solids, for long periods of storage. Their water solubility makes these compounds readily adaptable, for further syntheses, to reactions employing aqueous media. The corresponding esters, the acids which can readily be obtained by hydrolysis, and the alkali-metal enolates themselves, have utility as intermediates in the preparation of biologically active compounds such as cortisone and

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compounds such as the corresponding 21-glyoxalic acids and 21-acetoxy-3-hydroxypregnane-11,20-dione, as shown in Example 1A and 1B.

The novel compounds of the present invention which are of particular interest are those compounds having the above generic formula wherein M is sodium or potassium and R is lower-alkyl such as, for example, methyl, ethyl, propyl, isopropyl, butyl, amyl, hexyl, heptyl, octyl, and the like, with methyl and ethyl being preferred.

The starting compounds of the present invention are the 3-hydroxypregnane-11,20-diones which may be prepared by known procedure [Von Euw, Lardon and Reichstein, Helv. Chim. Acta, 27, 821 (1944)].

According to the method of the present invention, a 21-alkoxyoxalyl-3-hydroxyprogesterone alkali-metal enolate is prepared by mixing the selected 3-hydroxypregnane-11,20-dione with an alkyl di-ester of oxalic acid in the presence of an alkali-metal base.

In carrying out the novel process of the present invention, a 3-hydroxypregnane-11,20-dione is usually dissolved in the alkanol corresponding to the alkanol used in the formation of the selected ester of oxalic acid, or in a solvent which is non-reactive under the conditions of reaction, such as, for example, benzene or ether, and mixed with the selected alkyl di-ester of oxalic acid in the presence of an alkali-metal base. The di-esters of oxalic acid which are preferred in the method of the present invention are lower-alkyl esters containing from one to eight carbon atoms, inclusive. Of these the methyl and ethyl esters are preferred. Alkali-metal bases which may be used include the alkali-metal alkoxides, the alkali metals, the alkali-metal hydrides, sodium amide, tri-phenyl methyl sodium, and others. Of these the sodium and potassium alkoxides are preferred. The selected alkali-metal base catalyses the condensation of the alkyl di-ester of oxalic acid with the 3-hydroxypregnane-11,20-dione and contributes the alkali-metal moiety of the alkali-metal enolate. The alkali-metal alkoxide may be used solvent-free, dissolved or suspended in a non-reactive solvent, or in situ in the alkonal in which said alkali-metal alkoxide was formed. When potassium is used, it is usually used as the solution formed by its reaction with tertiary butyl alcohol according to procedure well known in the art.

The resulting reaction mixture is then allowed to stand at a temperature between about zero degrees centigrade and the boiling point of the reaction mixture, preferably at room tempera-

ture, for a period of between about one half hour and about ninety-six hours, usually about one to four hours.

The thus-produced alkali-metal enolate may be separated by the addition of a large volume of an organic solvent in which the alkali-metal enolate is insoluble, such as ether, for example. The thus-recovered 21-alkoxyoxalyl-3-hydroxypregnane-11,20-dione alkali-metal enolate is usually obtained as an amorphous solid, and is a stable form of the corresponding ester. Alternatively, it may be used, without isolation, as an intermediate in the synthesis of the corresponding 21-glyoxalic acid, or as an intermediate for the introduction of a 21-hydroxy or acyloxy group into 3-hydroxypregnane-11,20-dione as described in procedures A and B of Example 1.

The following examples are given to illustrate the method of the present invention and are not to be construed as limiting.

Example 1.—Sodium enolate of 21-ethoxyoxalyl-3α-hydroxypregnane-11,20-dione

To a mixture of 3.4 milliliters of a 3.4 N solution of methanolic sodium methoxide, 19.5 milliliters of dry benzene and 0.05 milliliters of absolute ethanol, said mixture having been distilled until approximately eight milliliters of distillate had been collected and the mixture then cooled, was added 2.3 milliliters of ethyl oxalate with stirring followed by a solution of 3.32 grams (0.01 mole) of 3α-hydroxypregnane-11,20-dione in a mixture of thirty milliliters of dry benzene and five milliliters of absolute ethanol. The reaction mixture was stirred for 85 minutes during which time some solid material precipitated. Sixty milliliters of anhydrous ether was then added thereto and the whole stirred for an additional hour whereafter an additional 100 milliliters of anhydrous ether was added thereto. The ivory colored sodium enolate of 21-ethoxyoxalyl - 3α - hydroxypregnane - 11,20 - dione thus-precipitated was filtered, washed with ether and after drying in a vacuum desiccator over Drierite (anhydrous calcium sulfate) was found to weigh 3.65 grams, a yield of 85 per cent of theoretical. The product melted above 250 degrees centigrade and the presence of a sodium enolate in the structure was verified by the extreme solubility of the product in water and by a positive ferric chloride test for enols as exhibited by the formation of a bright red color when the product was dissolved in aqueous and alcoholic solutions of ferric chloride. The theoretical structure was further verified by the conversion of the product to the 21-glyoxalic acid of 3α - hydroxypregnane - 11,20 - dione and to 21-acetoxy - 3α - hydroxypregnane - 11,20 - dione as shown below.

A.—21-GLYOXALIC ACID OF 3α-HYDROXYPREGNANE-11,20-DIONE

Five hundred and sixty milligrams of the sodium enolate of 21-ethoxyoxalyl-3α-hydroxypregnane-11,20-dione obtained above was dissolved in a solution of seventy milligrams of potassium hydroxide in fifteen milliliters of a solution composed of equal parts of water and alcohol, whereafter the whole was heated for fifteen minutes on a steam bath. The cooled solution was then filtered and upon acidification there was slowly deposited 345 milligrams of a white crystalline precipitate of the 21-glyoxalic acid of 3α-hydroxypregnane-11,20-dione which separated into two different crystalline modifications upon fractional crystallization from ether. The infrared analysis of said crystalline modifications in solution (chloroform) proved them to be identical compounds and verified their theoretical structure. The fraction more soluble in ether, after recrystallization from ten parts of acetic acid, melted at 218 degrees centigrade with effervescence, and the fraction less soluble in ether, after recrystallization from ten parts of acetic acid, melted at 235.5–236 degrees centigrade.

Analysis (lower melting sample): Per cent calculated for $C_{23}H_{32}O_6$: C, 68.29; H, 7.97. Found: C, 67.93; H, 7.65; C, 68.12; H, 7.87.

B.—3α-HYDROXY-21-ACETOXY-PREGNANE-11,20-DIONE

To a solution of 1.82 grams (0.004 mole) of the sodium salt of 21-ethoxyoxalyl-3α-hydroxypregnane-11,20-dione dissolved in 25 milliliters of methanol and cooled in an ice-salt bath was added dropwise, with stirring, over a period of approximately one hour, a solution of 1.05 grams (0.004 mole) of iodine dissolved in forty milliliters of methanol while maintaing the reaction temperature between minus fifteen and minus twenty degrees centigrade. The deep red reaction mixture thus-produced was stirred for eighty minutes at a temperature of about minus fifteen degrees centigrade whereafter 1.2 milliliters of a 3.4 N methanolic sodium methoxide solution was added thereto, causing the deep red color of the reaction mixture to disappear. Stirring was continued at zero degrees centigrade for one hour and the thus-produced 3α-hydroxy-21-iodo-pregnane-11,20-dione was precipitated as a yellow solid by the dropwise addition of 150 milliliters of water to the reaction mixture while maintaining the reaction mixture temperature at zero degrees centigrade for the hour required to complete the addition. Twenty grams of sodium chloride was then dissolved in the reaction mixture and the said yellow product filtered, washed with water and dried in a vacuum desiccator. The thus-isolated 3α-hydroxy-21-iodo-pregnane-11,20-dione was converted without further purification to 3α-hydroxy-21-acetoxy-pregnane-11,20-dione as shown below.

To a freshly prepared mixture composed of twenty grams of potassium bicarbonate, twelve grams of glacial acetic acid and ten milliliters of acetone was added the 3α-hydroxy-21-iodo-pregnane-11,20-dione obtained above dissolved in 100 milliliters of acetone. The mixture was heated under refluxing conditions for one hour whereafter the mixture was kept at room temperature for 2.5 days. The inorganic solids were removed by filtration and washed with 25 milliliters of acetone. The filtrate and wash were combined and the acetone removed by evaporation. The residue was extracted with three fifty milliliter portions of warm ethyl acetate which were then combined, washed with a dilute sodium thiosulfate solution and water, and finally dried over anhydrous sodium sulfate. The dry ethyl acetate was distilled in vacuo and the residue was dissolved in a small portion of benzene and chromatographed over 85 grams of 60–100 mesh Florisil (synthetic magnesium silicate). The column was developed with 100 milliliter portions of solvents of the following composition and order: benzene, seven portions Skelly Solve B (hexane hydrocarbons) plus five per cent acetone, four portions of Skelly Solve B plus ten per cent acetone, eight portions of Skelly Solve B plus fifteen per cent acetone, eight portions of Skelly Solve B plus twenty per cent acetone, and one portion each of

Skelly Solve B plus fifty per cent acetone. The first five portions of Skelly Solve B plus twenty per cent acetone eluates were combined and the solvent evaporated. The 3α-hydroxy - 21 - acetoxy - pregnane - 11,20 - dione residue melted at 139–140 degrees centigrade (corrected) and had a rotation $[\alpha]_D$ of plus 105 degrees in acetone. Infrared and carbon-hydrogen analyses confirmed the theoretical structure.

Analysis: Per cent calculated for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.90; H, 8.85; C, 70.91; H, 8.86.

Example 2.—Sodium enolate of 21-ethoxyoxalyl-3β-hydroxypregnane-11,20-dione

Using essentially the procedure described in Example 1, 3β-hydroxypregnane-11,20-dione is converted to the sodium enolate of 21-ethoxyoxalyl-3β-hydroxypregnane-11,20-dione by reaction with ethyl oxalate and sodium in absolute ethanol. The resulting sodium enolate is converted, as with the 3α-hydroxy compound, to the 21-glyoxalic acid of 3β-hydroxypregnane-11,20-dione and 21-acetoxy-3β-hydroxypregnane-11,20-dione according to the procedure of Example 1A and 1B.

Example 3.—Sodium enolate of 21-methoxyoxalyl-3α-hydroxypregnane-11,20-dione

Using essentially the procedure described in Example 1, 3α-hydroxypregnane-11,20-dione is converted to the sodium enolate of 21-methoxyoxalyl-3α-hydroxypregnane-11,20-dione by reaction with methyl oxalate and sodium in absolute methanol. The resulting sodium enolate is converted, as with the 21-ethoxyoxalyl compound, to the 21-glyoxalic acid of 3α-hydroxypregnane-11,20-dione and 21-acetoxy-3α-hydroxypregnane-11,20-dione according to the procedure of Example 1A and 1B.

Example 4.—Sodium enolate of 21-methoxyoxalyl-3β-hydroxypregnane-11,20-dione

Using essentially the procedure described in Example 1, 3β-hydroxypregnane-11,20-dione is converted to the sodium enolate of 21-methoxyoxalyl-3β-hydroxypregnane-11,20-dione by reaction with methyl oxalate and sodium in absolute methanol. The resulting sodium enolate is converted, as with the 3α-hydroxy compound, to the 21-glyoxalic acid of 3β-hydroxypregnane-11,20-dione and 21-acetoxy-3β-hydroxypregnane-11,20-dione according to the procedure of Example 1A and 1B.

Example 5.—Potassium enolate of 21-ethoxyoxalyl-3α-hydroxypregnane-11,20-dione

Using essentially the procedure described in Example 1, 3α-hydroxypregnane-11,20-dione is converted to the potassium enolate of 21-ethoxyoxalyl-3α-hydroxypregnane-11,20-dione by reaction with ethyl oxalate and potassium in tertiary butyl alcohol. The resulting potassium enolate is converted, as with the corresponding sodium enolate, to the 21-glyoxalic acid of 3α-hydroxypregnane-11,20-dione and 21-acetoxy-3α-hydroxypregnane-11,20-dione according to the procedure of Example 1A and 1B.

Example 6.—Sodium enolate of 21-ethoxyoxalyl-3α-hydroxypregnane-11,20-dione

Using essentially the procedure described in Example 1, 3α-hydroxypregnane-11,20-dione is converted to the sodium enolate of 21-ethoxyoxalyl-3α-hydroxypregnane-11,20-dione by reaction with ethyl oxalate and sodium amide in benzene.

In a manner similar to Examples 1 through 6, the following compounds are prepared by reaction of the selected 3-hydroxy-pregnane-11,20-dione with the appropriate alkyl oxalate and sodium or potassium alkoxide in an alkanol or non-reactive solvent medium: sodium enolate of 21-propoxyoxalyl - 3α - hydroxypregnane - 11,20-dione and 21-propoxyoxalyl-3β-hydroxypregnane-11,20-dione, sodium enolate of 21-butoxyoxalyl-3α-hydroxypregnane-11,20-dione and 21-butoxyoxalyl - 3β - hydroxypregnane - 11,20-dione, sodium enolate of 21-amyloxyoxalyl-3α-hydroxypregnane-11,20-dione and 21-amyloxyoxalyl - 3β - hydroxypregnane - 11,20 - dione, sodium enolate of 21-hexyloxyoxalyl-3α-hydroxypregnane-11,20-dione and 21-hexyloxyoxalyl-3β-hydroxypregnane-11,20-dione, sodium enolate of 21 - heptyloxyoxalyl - 3α - hydroxypregnane-11,20-dione and 21-heptyloxyoxalyl-3β-hydroxypregnane-11,20-dione, sodium enolate of 21-octyloxyoxalyl - 3α - hydroxypregnane - 11,20-dione and 21-octyloxyoxalyl-3β-hydroxypregnane-11,20-dione, the potassium analogues of these and like compounds, and others.

It is to be understood that the invention is not to be limited to the exact details or exact compounds shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the scope of the appended claims.

We claim:

1. A 21 - alkoxyoxalyl - 3 - hydroxypregnane-11,20-dione alkali-metal enolate, wherein the alkyl radical of the alkoxy group contains from one to eight carbon atoms, inclusive.

2. The sodium enolate of a 21-alkoxyoxalyl-3-hydroxypregnane-11,20-dione, wherein the alkyl radical of the alkoxy group contains from one to eight carbon atoms, inclusive.

3. The potassium enolate of a 21-alkoxyoxalyl-3-hydroxypregnane-11,20-dione, wherein the alkyl radical of the alkoxy group contains from one to eight carbon atoms, inclusive.

4. The sodium enolate of 21-methoxyoxalyl-3α-hydroxypregnane-11,20-dione.

5. The sodium enolate of 21-ethoxyoxalyl-3α-hydroxypregnane-11,20-dione.

6. The sodium enolate of 21-methoxyoxalyl-3β-hydroxypregnane-11,20-dione.

7. The sodium enolate of 21-ethoxyoxalyl-3β-hydroxypregnane-11,20-dione.

8. The potassium enolate of 21-ethoxyoxalyl-3α-hydroxypregnane-11,20-dione.

9. A process for the production of a 21-alkoxyoxalyl - 3 - hydroxypregnane-11,20-dione alkali-metal enolate which includes the step of mixing a 3-hydroxypregnane-11,20-dione with an alkyl di-ester of oxalic acid in the presence of an alkali-metal base, and continuing the reaction at a temperature between about zero degrees centigrade and the boiling point of the reaction mixture, to produce the desired 21-alkoxyoxalyl-3-hydroxypregnane-11,20-dione alkali-metal enolate.

10. A process for the production of a 21-alkoxyoxalyl-3-hydroxypregnane-11,20-dione alkali-metal enolate which includes: mixing a 3-hydroxypregnane-11,20-dione with an alkyl di-ester of oxalic acid wherein the alkyl radicals of the di-ester of oxalic acid each contain from one to eight carbon atoms, inclusive, in the presence

of an alkali-metal base, continuing the reaction at a temperature between about zero degrees centigrade and the boiling point of the reaction mixture, and separating the thus-produced 21-alkoxyoxalyl-3-hydroxypregnane-11,20-dione.

11. A process for the production of a 21-alkoxyoxalyl-3-hydroxypregnane-11,20-dione alkali-metal enolate which includes: mixing a 3-hydroxypregnane-11,20-dione with an alkyl di-ester of oxalic acid in the presence of an alkali-metal alkoxide, wherein the alkyl radicals of the di-ester of oxalic acid and the alkali-metal alkoxide each contain from one to eight carbon atoms, inclusive, continuing the reaction at a temperature between zero degrees centigrade and the boiling point of the reaction mixture, and separating the thus-produced 21-alkoxyoxalyl-3-hydroxypregnane - 11,20 - dione alkali - metal enolate.

12. A process for the production of a 21-alkoxyoxalyl-3-hydroxypregnane-11,20-dione alkali-metal enolate which includes: mixing a 3-hydroxypregnane-11,20-dione with an alkyl di-ester of oxalic acid in the presence of a solution of an alkali metal in an alkanol, the alkyl radicals of the di-ester of oxalic acid and the alkanol each containing from one to eight carbon atoms, inclusive, continuing the reaction at a temperature between zero degrees centigrade and the boiling point of the reaction mixture, and separating the thus-produced 21-alkoxyoxalyl-3-hydroxypregnane - 11,20 - dione alkali - metal enolate.

13. A process for the production of the sodium enolate of 21-ethoxyoxalyl-3α-hydroxypregnane-11,20-dione which includes: mixing 3α-hydroxypregnane-11,20-dione with diethyl oxalate in the presence of sodium ethoxide, continuing the reaction at a temperature between about room temperature and the boiling point of the reaction mixture, and separating the thus-produced sodium enolate of 21-ethoxyoxalyl - 3α - hydroxypregnane-11,20-dione.

14. A process for the production of the sodium enolate of 21 - methoxyoxalyl-3α-hydroxypregnane-11,20-dione which includes: mixing 3α-hydroxypregnane - 11,20 - dione with dimethyl oxalate in the presence of sodium methoxide, continuing the reaction at a temperature between about room temperature and the boiling point of the reaction mixture, and separating the thus-produced sodium enolate of 21-methoxyoxalyl-3α-hydroxypregnane-11,20-dione.

15. A process for the production of the sodium enolate of 21-ethoxyoxalyl - 3β - hydroxypregnane-11,20-dione which includes: mixing 3β-hydroxypregnane-11,20-dione with diethyl oxalate in the presence of sodium ethoxide, continuing the reaction at a temperature between about room temperature and the boiling point of the reaction mixture, and separating the thus-produced sodium enolate of 21-ethoxyoxalyl-3β-hydroxypregnane-11,20-dione.

16. A process for the production of the sodium enolate of 21 - methoxyoxalyl-3β-hydroxypregnane-11,20-dione which includes: mixing 3β-hydroxypregnane - 11,20 - dione with dimethyl oxalate in the presence of sodium methoxide, continuing the reaction at a temperature between about room temperature and the boiling point of the reaction mixture, and separating the thus-produced sodium enolate of 21-methoxyoxalyl-3β-hydroxypregnane-11,20-dione.

17. A process for the produtcion of the potassium enolate of 21-ethoxyoxalyl-3β-hydroxypregnane-11,20-dione which includes: mixing 3α-hydroxypregnane - 11,20 - dione with diethyl oxalate in the presence of a solution of potassium in tertiary butyl alcohol, continuing the reaction at a temperature between about room temperature and the boiling point of the reaction mixture, and separating the thus-produced potassium enolate of 21-ethoxyoxalyl-3α-hydroxypregnane-11,20-dione.

References Cited in the file of this patent

UNITED STATES PATENTS

Number	Name	Date
2,265,417	Bockmuhl	Dec. 9, 1941
2,541,104	Sarett	Feb. 13. 1951