

PATENT SPECIFICATION

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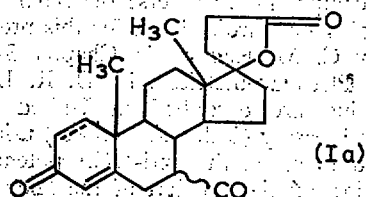
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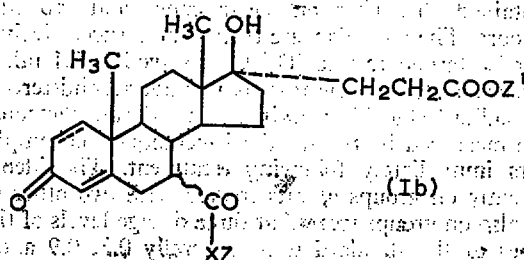
(54) 17-HYDROXY-7-(LOWER ALKOXY) CARBONYL-3-OXO-17 α -PREGN-4-ENE-21-CARBOXYLIC ACID γ -LACTONES AND CONGENERS

(71) We, G. D. SEARLE & CO., a corporation organised and existing under the laws of the State of Delaware United States of America of P.O. Box 5110 Chicago, Illinois, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to 17-hydroxy-7-(lower alkoxy)carbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactones and congeners. More particularly, this invention provides novel compounds of the general structural formulas



and

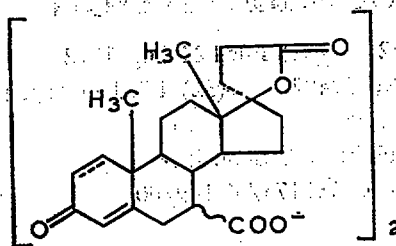


wherein Z is hydrogen, alkali metal, alkaline-earth metal/2, ammonium or alkyl; Z' is hydrogen, alkali metal, alkaline-earth metal/2 or ammonium when Z is alkyl; Z' is identical to Z and Z is hydrogen, alkali metal, alkaline-earth metal/2 or ammonium; the dotted line indicates the optional presence of a Δ^1 unsaturated linkage; the wavy line indicates the alternative α and β configurations; and X is oxygen, with the proviso that when Z is alkyl and the 1,2-linkage is saturated, X in formula (Ia) can also be sulfur.

Preferred compounds of formulas (Ia) and (Ib) are those compounds wherein the substituent at the 7-position is a 7 α -alkoxycarbonyl radical and Z' is alkali metal or alkaline-earth metal/2, especially preferred compounds being further characterized by a saturated 1,2-linkage.

Preferred alkali metals and alkaline-earth metals encompassed by the Z and Z' terms include potassium, sodium, lithium, magnesium and calcium. Those skilled in the art will recognize that the term "alkaline-earth metal/2" is dictated by the fact that alkaline-earth metals are divalent, whereas the other groups represented by Z and Z' are monovalent; and when, for example, Z represents Ca/2 and X is oxygen in formula (Ia), the contemplated salts are more conventionally depicted thus

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Among the alkyl radicals represented by Z, lower alkyl radicals are preferred, i.e. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, *tert*-butyl, pentyl, neopentyl, hexyl, isohexyl, heptyl, and like monovalent, saturated, acyclic, straight- or branched-chain hydrocarbon groupings of empirical formula



wherein n represents an integer less than 8.

Equivalent to the compounds of formulas (Ia) and (Ib) for the purposes of this invention are solvates thereof in which biologically insignificant amounts of solvent are present.

The foregoing compounds are useful by reason of their valuable biological properties. Thus, for example, they are diuretic. They reverse the effect of desoxycorticosterone acetate (DCA) on urinary sodium and potassium. They also possess blood pressure lowering properties.

The capacity of the instant compounds to reverse the renal electrolyte effects of DCA is evident from the results of a standardized test for this property carried out in rats substantially as described by C. M. Kagawa in Chapter 34 of Volume II of "Evaluation of Drug Activities: Pharmacometrics", by D. R. Laurence and A. L. Bacharach. Details of such testing are described in United States Patent No. 3,422,096. Additionally, a 6 point bioassay (2 drugs $\times$ 3 doses) using the same general test procedure has been employed to assess the anti-DCA potency of representative compounds of the present invention relative to that of the known diuretic, spironolactone. Details of that bioassay are as follows:

Groups of 4 male rats, each weighing between 150 and 200 grams, were adrenalectomized and maintained thereafter on sugar cubes and tap water *ad libitum* for approximately 24 hours. The animals were then treated successively with the following: 12 μ g. of desoxycorticosterone acetate (DCA) dissolved in 0.1 ml. of corn oil, injected subcutaneously; a selected dose of the test compound, administered orally; and 2.5 ml. of 0.85% aqueous sodium chloride solution, injected subcutaneously. Urinary sodium and potassium were measured by the standard techniques on samples of urine collected during the 4 hours immediately following treatment. The identical procedure was carried out concurrently on groups of rats treated with two other selected doses of the test compound and also on groups treated at three dosage levels of the standard, spironolactone. The dosages of the standard were generally 0.3, 0.9 and 2.7 mg./rat, while those of the test compound were selected such that they produced an average biological response approximately equal to that of the standard. Based upon this 6 point bioassay, using an increase in the urinary log $(Na \times 10)/K$ ratio as the index of anti-DCA activity, it was determined that a number of representative compounds of the present invention were more potent than spironolactone. Especially potent in this bioassay were 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone and 7 α -ethoxycarbonyl-17-hydroxy-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone.

The compounds of formula (Ia) where X is oxygen, Z is alkyl and the 1,2-linkage is saturated can be prepared by contacting 4 α ,7 α -carbonyl-5-cyano-17-hydroxy-3-oxo-5 β ,17 α -pregnane-21-carboxylic acid γ -lactone (which is disclosed and claimed in copending Application No. 1390/74) Serial No. 1368006) with an alkali metal alkoxide to afford a mixture of the 7 α - and 7 β -alkoxycarbonyl compounds, followed by isolation of the desired 7 α or 7 β isomer. The alkali metal alkoxide is preferably a sodium or potassium alkoxide and can be conveniently prepared, if so desired, directly in the reaction mixture from an alkali metal and an alkanol, preferred alkanols for this purpose being methanol and ethanol. After heating the metal and alkanol with the 4 α ,7 α -carbonyl compound, the 7 α and 7 β epimers which are obtained can be separated by fractional crystallization and chromatography on dry silica gel. The 4 α ,7 α -carbonyl

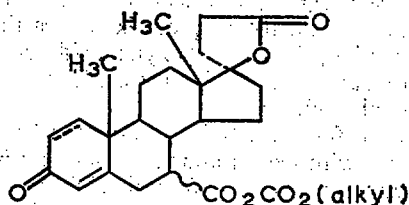
starting material used in this reaction can be prepared by heating 17-hydroxy-3-oxo-17 α -pregna-4,6-diene-21-carboxylic acid γ -lactone with an alkali metal cyanide such as potassium cyanide in a suitable solvent under slightly basic conditions, followed by heating the resultant 7 α -4-aminomethylidene-5-cyano-17-hydroxy-3-oxo-5 β ,17 α -pregnane-21-carboxylic acid γ -lactone with very dilute aqueous mineral acid.

The aforementioned 4 α ,7 α -carbonyl starting material can also be utilized in the preparation of the 7 α compound of formula (Ia) wherein X is oxygen, Z is hydrogen and the 1,2-linkage is saturated. Thus, contacting that starting material with potassium hydroxide in methanol, followed by alkaline hydrolysis and subsequent treatment with mineral acid affords the desired 7 α -acid. The reaction with potassium hydroxide in methanol is conveniently conducted at the reflux temperature. The subsequent alkaline hydrolysis can be readily achieved using potassium hydroxide in aqueous methanol, while hydrochloric acid is conveniently employed as the mineral acid for the final step.

Dehydrogenation of a compound of formula (Ia) wherein X is oxygen, Z is alkyl and the 1,2-linkage is saturated affords the corresponding compound of formula (Ia) wherein the 1,2-linkage is unsaturated. The dehydrogenation is effected by use of a reagent conventional for the conversion of a 3-keto- Δ^4 -steroid to a 3-keto- $\Delta^{1,4}$ -steroid. A preferred reagent is 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, which is conveniently heated with the Δ^4 starting material in a suitable solvent such as benzene, xylene or dioxane. Another reagent suitable for this purpose is selenium dioxide, which is generally heated with the Δ^4 starting material in *t*-butanol.

Alkaline hydrolysis of a Δ^4 or $\Delta^{1,4}$ compound of formula (Ia) wherein X is oxygen and Z is alkyl, followed by treatment with mineral acid, affords the corresponding compound of formula (Ia) wherein Z is hydrogen. The hydrolysis is conveniently effected by heating the starting material with aqueous sodium hydroxide or aqueous methanolic potassium hydroxide. Typically, hydrochloric acid is employed for the subsequent acid treatment.

Another synthetic method, which affords the Δ^4 - and $\Delta^{1,4}$ -7-alkoxycarbonyl compounds of formula (Ia), consists of contacting an active acylating derivative of a compound of formula (Ia) wherein X is oxygen and Z is hydrogen with an alkanol. In one embodiment, this method utilizes, as the active acylating derivative, a carbonic anhydride of the general formula



wherein the dotted line indicates the optional presence of a Δ^1 unsaturated linkage; and the wavy line indicates the alternative α and β configurations. The compounds of formula (II) can be readily synthesized by contacting the corresponding 7-carboxylic acids of formula (Ia) with an alkylchloroformate such as isobutylchloroformate or ethylchloroformate in a suitable solvent, *e.g.* tetrahydrofuran, in the presence of a tertiary amine, *e.g.* 4-methylmorpholine or triethylamine. Although it is frequently preferable to isolate the anhydride prior to reacting it with an alkanol, it is not essential to do so. This process is a highly desirable route to the esters of the present invention, especially to those wherein Z contains two or more carbon atoms.

In another embodiment of the method employing an active acylating derivative of a 7-acid of formula (Ia), the active acylating derivative is a mixed anhydride such as the anhydride formed by reacting acetic anhydride with the aforementioned steroidal acid. In yet another embodiment of that general method, the active acylating derivative is an acid chloride. The acid chloride can be prepared by converting the steroidal acid to the corresponding potassium 7-carboxylate and then reacting that salt with oxalyl chloride.

Appropriate modification of the method using an active acylating derivative which is described above will afford the thio esters of formula (Ia). Thus, one of the aforementioned active acylating derivatives of a compound of formula (Ia) wherein X is oxygen, Z is hydrogen and the 1,2-linkage is saturated, *e.g.* a Δ^4 compound of formula (II), is contacted with an alkane-thiol to afford the desired 7-thio ester.

Reaction of a Δ^4 or $\Delta^{1,4}$ compound of formula (Ia) wherein X is oxygen and Z is alkyl or hydrogen with, respectively, one or two equivalents of an appropriate base, in an aqueous medium, affords the corresponding mono- or bis-(alkali metal) or (alkaline-earth metal/2) salt of formula (Ib). If desired, the resultant salt of formula (Ib) can be exposed to a proton source for a short period of time, thus affording the corresponding mono- or dicarboxylic acid of formula (Ib). Thus, when the starting material of formula (Ia) is a 7-ester, that material can be heated with one equivalent of an alkali metal or alkaline earth metal hydroxide, in an aqueous medium, to afford the corresponding compound of formula (Ib) wherein Z is alkyl and Z' is alkali metal or alkaline-earth metal/2. Preferably, this reaction is carried out in an aqueous alkanol containing the same number of carbon atoms as is present in the alkoxy group of the 7-alkoxy carbonyl grouping of the starting material, i.e. the salt of a 7-methoxy-carbonyl compound is prepared in methanol, the salt of a 7-ethoxy-carbonyl compound is prepared in ethanol and so forth, to ensure retention of the starting material's ester grouping in the final product. When the starting material is an acid, that substance is heated with two equivalents of an alkali metal or alkaline earth metal hydroxide in an aqueous medium, to afford the corresponding compound of formula (Ib) wherein both Z and Z' are alkali metal or alkaline-earth metal/2. An aqueous alkanol can be conveniently employed as the solvent in this case. Subsequent brief contact of the salts with a mineral acid, e.g. hydrochloric acid, under very dilute conditions, affords the corresponding 21-mono- and 7,21-dicarboxylic acids.

Contacting a compound of formula (Ia) or (Ib) wherein X is oxygen, Z is hydrogen or alkyl and Z' is hydrogen, Z and Z' being selected so that the molecule contains at least one acid hydrogen, with a quantity of an appropriate base equivalent to the amount of acid hydrogen present, in an aqueous medium, affords the corresponding mono- or bis(alkali metal) or alkaline-earth metal/2 salt of formula (Ia) or (Ib). Thus, a 7-acid of formula (Ia) can be reacted with one equivalent of an appropriate base, e.g. an alkali metal bicarbonate or alkaline-earth metal hydroxide, in an aqueous medium, conveniently in an aqueous alkanol, to yield the corresponding salt of formula (Ia). Similarly, reaction of a 7-ester of formula (Ib) having an acid group at the 21-position with one equivalent of a suitable base, e.g. an alkali metal or alkaline earth metal hydroxide, in an aqueous medium, preferably in an aqueous alkanol containing the same number of carbon atoms as is present in the starting material's 7-alkoxy grouping, will afford the desired 7-ester 21-salt. In a similar manner, the compounds of formula (Ib) wherein both X and Z' are alkali metal or alkaline-earth metal/2 can be prepared by warming the corresponding 7,21-dicarboxylic acid with two equivalents of the appropriate base, e.g. an alkali metal or alkaline-earth metal hydroxide, in an aqueous medium, e.g. an aqueous alkanol.

The ammonium salts of formulas (Ia) and (Ib) can be prepared from the corresponding acids by treatment with excess ammonia, suitably in an organic solvent such as 2-propanol. In this manner, a 7-acid of formula (Ia) is converted to the corresponding ammonium 7-carboxylate of formula (Ia); a 7-ester of formula (Ib) having an acid group at the 21-position is converted to the corresponding 7-ester 21-salt; and a 7,21-dicarboxylic acid of formula (Ib) is converted to the corresponding 7,21-bis(ammonium) salt.

The following examples illustrate the invention. In these examples, temperatures are given in degrees centigrade ($^{\circ}\text{C}$.) and amounts of materials in parts by weight unless parts by volume are specified. The relationship between parts by weight and parts by volume is the same as that existing between grams and milliliters. Specific rotations refer to the D line of sodium, the solvent being chloroform at room temperature unless otherwise indicated.

EXAMPLE 1

A solution consisting of approximately 51 parts of 17-hydroxy-3-oxo-17 α -pregna-4,6-diene-21-carboxylic acid γ -lactone, 50 parts of potassium cyanide, 72 parts of ethyl acetate, 454 parts of methanol and 160 parts of water was heated at the boiling point under reflux with stirring for four and one-half hours, then was allowed to stand at room temperature overnight. Organic solvents were thereupon removed by vacuum distillation, the oily residue was diluted with 500 parts of water, and the pH was adjusted to 7 by slowly introducing 20% hydrochloric acid. Hydrogen cyanide was evolved, and precipitation occurred. The precipitate was filtered off, dried in air, and taken up in ethyl acetate. The ethyl acetate solution was extracted with 20% hydrochloric acid, and residual ethyl acetate was removed from the extract by bubbling nitrogen therethrough. The extract was thereupon cooled to 0°C . and neutralized with sodium hydroxide. The resultant tan precipitate was filtered off, washed well with

water, dried in air, and recrystallized from acetone to give 7 α ,4-aminomethylidene-5-cyano-17 α -hydroxy-3-oxo-5 β ,17 α -pregnane-21-carboxylic acid γ -lactone melting at 278—283°C.

A slurry of approximately 21 parts of 7 α ,4-aminomethylidene-5-cyano-17-hydroxy-3-oxo-5 β ,17 α -pregnane-21-carboxylic acid γ -lactone in 350 parts of 3% hydrochloric acid was heated at 90—95°C. with occasional stirring for four and one-half hours, then cooled. Insoluble solids were separated by filtration, washed to neutrality with water, dried in air, and recrystallized from 2-propanol to give 4 α ,7 α -carbonyl-5-cyano-17-hydroxy-3-oxo-5 β ,17 α -pregnane-21-carboxylic acid γ -lactone melting at 284—289°C.

To 185 parts of sodium metal was added 4200 parts of methanol at a rate such that rapid refluxing was maintained. When the addition was complete, refluxing was continued for 3 hours, via external heating, whereupon 14,200 parts of methanol followed by 197 parts of 4 α ,7 α -carbonyl-5-cyano-17-hydroxy-3-oxo-5 β ,17 α -pregnane-21-carboxylic acid γ -lactone was introduced. The resultant solution was heated at the boiling point under reflux with stirring in a nitrogen atmosphere for 22 hours, whereupon solvent was removed by vacuum distillation. The oily residue was taken up in 4000 parts of water. The aqueous solution was diluted with 4000 parts of acetone and then acidified with 10% hydrochloric acid. After 30 minutes, the acetone was removed by vacuum distillation, and the residue was extracted with ethyl acetate. The extract was washed well with aqueous 5% potassium bicarbonate and then with water, next dried over magnesium sulfate and sodium sulfate, and finally stripped of solvent by vacuum distillation. The resultant oil was dissolved in a minimum amount of methanol. Colorless 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone crystallized out of the methanol solution and was isolated by filtration and dried in air. It melts at 190—192°C.

The mother liquor was chromatographed on silica gel, using benzene and mixtures thereof with increasing amounts of ethyl acetate as developing solvents. From an eluate comprising 15% ethyl acetate in benzene, on evaporation of solvent and recrystallization of the residue from methanol, 17-hydroxy-7 β -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone melting at 238—240°C. was obtained.

EXAMPLE 2

A solution of 43 parts of 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone and 135 parts of aqueous 4% potassium hydroxide in 2000 parts of methanol, protected by a nitrogen atmosphere, was warmed to 40°C. during 5 minutes and thereafter stirred at ambient temperature overnight. The solution was thereupon heated at the boiling point under reflux for 2 hours, at which point solvent was removed by vacuum distillation and the residual solution was diluted with 3000 parts of water. The solution thus obtained was washed well with ethyl acetate and then distilled, leaving a gummy residue which was taken up in a minimum amount of ethanol. Sufficient ethyl acetate was added to precipitate potassium 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylate as a white flocculent solid.

EXAMPLE 3

To a solution of 1 part of potassium 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylate in 70 parts of water was added 20 parts of 5% hydrochloric acid. The resultant precipitate was filtered off, washed with water, and dried in air. The material thus isolated was 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid.

EXAMPLE 4

A solution of approximately 1 part of 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone and 12 parts of aqueous 5% potassium hydroxide in 8 parts of methanol was heated at the boiling point under reflux in a nitrogen atmosphere for 6 hours, whereupon methanol was removed by vacuum distillation and the aqueous residue was diluted with 25 parts of acetone. The resultant mixture was acidified with 3% hydrochloric acid, allowed to stand at room temperature for 20 minutes and then concentrated to one-fifth volume by vacuum distillation. Insoluble solids were filtered off and taken up in 50 parts of ethyl acetate. Concentration of the ethyl acetate solution to one-half volume by vacuum distillation resulted in precipitation of hydrated 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone, which was isolated by filtration. Additional product was isolated by extracting the filtrate with aqueous 5% potassium bicarbonate, acidifying the extract with 3% hydrochloric acid, again concentrating by vacuum distillation until precipitation.

of the product occurred, and filtering. Water of crystallization was removed from the hydrate thus produced by heating *in vacuo* at around 80°C., affording anhydrous product melting at 266—270°C.

EXAMPLE 5
A solution of 412 parts of 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone monohydrate and 100 parts of potassium bicarbonate in a mixture of 7900 parts of methanol and 12,000 parts of water was stirred under nitrogen at room temperature overnight, then heated at 40°C. for 30 minutes. Substantially all of the liquids were thereupon removed by vacuum distillation, leaving a yellow oil which was azeotropically dried by distilling ethanol therefrom. Trituration of the dried oil with ethyl acetate afforded potassium 21-carboxy-17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α -carboxylate γ -lactone as a colorless solid which was isolated by filtration and dried in air.

Substitution of 84 parts of sodium bicarbonate in the above procedure afforded sodium 21-carboxy-17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α -carboxylate γ -lactone.

EXAMPLE 6
A solution of 106 parts of 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone monohydrate in 730 parts of aqueous 4% potassium hydroxide was diluted with 2 volumes of water. The resultant solution was heated at 90—95°C. for 30 minutes, then stripped of water by vacuum distillation. The residue was extracted with 2-propanol. The propanol solution was filtered and, in turn, stripped of solvent by vacuum distillation, leaving a yellow powder which was dried *in vacuo* at 65°C. for 24 hours, then redissolved in 10,000 parts of hot 2-propanol. This solution was filtered, and the filtrate was concentrated to one-fourth volume by vacuum distillation. The precipitate thrown down as the concentrate cooled was dipotassium 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylate dihydrate, which was filtered off and dried in air. Water of crystallization was removed from the dihydrate by heating *in vacuo* at around 80°C.

EXAMPLE 7

To a solution of 2 parts of dipotassium 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylate dihydrate in 80 parts of water was added 10 parts of 5% hydrochloric acid. The colorless precipitate which resulted was filtered off, washed with water, and dried in air. The product thus isolated was 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone monohydrate.

EXAMPLE 8
To a solution of 6 parts of 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone monohydrate in approximately 15 parts of triethylamine and 150 parts of chloroform maintained at 0°C. was added approximately 7 parts of ethyl chloroformate. The resultant solution was allowed to warm to room temperature and stirred overnight, whereupon solvents were removed by vacuum distillation. The brown gummy residue was redissolved in a mixture of approximately 4 parts of triethylamine and 150 parts of chloroform. To this solution was added 5 parts of ethanethiol. The resultant solution was stirred at room temperature overnight. Solvents were then again removed by vacuum distillation, and the residue was taken up in chloroform. The chloroform solution was washed with approximately 3% hydrochloric acid and then with water, dried over sodium sulfate, and stripped of chloroform by vacuum distillation. The residue was chromatographed on dry silica gel, using 12% ethyl acetate in benzene as developing solvent. Upon evaporation of the solvent, 7 α -ethylthiocarbonyl-17-hydroxy-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone melting at 202—204°C. was obtained.

EXAMPLE 9
A solution of 14 parts of 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone and 11 parts of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone in 1800 parts of benzene was heated at the boiling point under reflux with stirring in a nitrogen atmosphere for 20 hours, then diluted with approximately 1000 parts of ether and filtered. The filtrate was washed with aqueous 2% sodium sulfite until the washes were colorless, whereupon it was washed with water, dried over sodium sulfate and magnesium sulfate, and stripped of solvent by vacuum distillation. The residual yellow oil was chromatographed on dry silica gel, using 12% ethyl acetate in benzene as developing solvent. Upon evaporation of the solvent and recrystallization of the

residue from ether, 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregna-1,4-diene-21-carboxylic acid γ -lactone tetartohydrate melting at 217–222°C. was obtained. The one-fourth mole of water of crystallization can be removed by heating *in vacuo* at around 80°C.

EXAMPLE 10

A solution of 1 part of 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregna-1,4-diene-21-carboxylic acid γ -lactone tetartohydrate and 12 parts of aqueous 5% potassium hydroxide in 20 parts of methanol was heated at the boiling point under reflux for 6 hours. Methanol was thereupon removed by vacuum distillation; and the aqueous residue was diluted with 25 parts of acetone, adjusted to pH 4 with 3% hydrochloric acid, and allowed to stand at room temperature for 20 minutes. Sufficient liquid was then removed by vacuum distillation to bring about precipitation. The precipitate was filtered off and taken up in ethyl acetate. The ethyl acetate solution was extracted with aqueous 5% potassium bicarbonate. The bicarbonate extract was acidified and then concentrated by vacuum distillation to the point of incipient precipitation. The colorless precipitate which formed on standing was filtered off and dried in air. The product thus isolated was 17-hydroxy-3-oxo-17 α -pregna-1,4-diene-7 α ,21-dicarboxylic acid γ -lactone.

EXAMPLE 11

A solution of 100 parts of 17-hydroxy-3-oxo-17 α -pregna-1,4-diene-7 α ,21-dicarboxylic acid γ -lactone and 744 parts of aqueous 4% potassium hydroxide in 4000 parts of methanol was heated at the boiling point under reflux for 2 hours. Substantially all of the liquids were removed from the resultant solution by vacuum distillation, and the yellow gummy residue was further dried azeotropically by distilling ethanol therefrom. The colorless residue thus obtained was recrystallized from ethyl acetate to give dipotassium 17-hydroxy-3-oxo-17 α -pregna-1,4-diene-7 α ,21-dicarboxylate.

EXAMPLE 12

Substitution of 2 parts of dipotassium 17-hydroxy-3-oxo-17 α -pregna-7 α ,21-dicarboxylate in the procedure of Example 7 afforded 17-hydroxy-3-oxo-17 α -pregna-1,4-diene-7 α ,21-dicarboxylic acid.

EXAMPLE 13

To 18 parts of sodium metal was added 840 parts of absolute ethanol at a rate such that rapid refluxing was maintained. When the addition was complete, refluxing was continued for 3 hours via external heating, whereupon 14,000 parts of ethanol followed by approximately 20 parts of 4 α ,7 α -carbonyl-5-cyano-17-hydroxy-3-oxo-5 β ,17 α -pregnane-21-carboxylic acid γ -lactone was introduced. The resultant solution was heated at the boiling point under reflux with stirring in a nitrogen atmosphere for 21 hours, then cooled and diluted with 10 volumes of water. Solvent was removed by vacuum distillation. An equal volume of acetone was added to the residue, followed by sufficient 3% hydrochloric acid to induce acidity. The resultant mixture was stripped of acetone by vacuum distillation, and the residual aqueous gum was extracted with dichloromethane. The dichloromethane extract was dried over sodium sulfate and magnesium sulfate, whereupon solvent was distilled off *in vacuo* and the residual yellow foam chromatographed on dry silica gel, using 10% ethyl acetate in benzene as developing solvent. Upon evaporation of solvent and recrystallization of the residue from petroleum solvent boiling in the range 95–127°C., 7 α -ethoxycarbonyl-17-hydroxy-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone melting at 143–145°C. was obtained. The mother liquor was chromatographed on silica gel, using benzene and mixtures thereof with increasing amounts of ethyl acetate as developing solvents. From an eluate comprising 15% ethyl acetate in benzene, on evaporation of solvent, 7 β -ethoxycarbonyl-17-hydroxy-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone was obtained as the residue.

EXAMPLE 14

To a solution of 80 parts of 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone monohydrate and 20 parts of 4-methylmorpholine in 600 parts of tetrahydrofuran at –15°C. under nitrogen was added, with stirring, 28 parts of isobutyl chloroformate. A white precipitate was thrown down. After 5 minutes, 640 parts of

2-propanol was introduced; and the resultant mixture was filtered in a nitrogen atmos-

phere. The filtrate was stripped of solvent by vacuum distillation, and the oily brown residue was taken up in 1560 parts of 2-propanol. This solution was heated at the boiling point under reflux for 6 hours, whereupon 1 part of imidazole was introduced. Boiling under reflux was resumed for a period of 18 hours, at which point 2000 parts of water was introduced. The resultant mixture was boiled under reflux for 35 hours, then freed of solvent by vacuum distillation. The gummy residue was extracted with ethyl acetate. The extract was thoroughly washed with aqueous 5% potassium bicarbonate, and then with water, dried over sodium sulfate and magnesium sulfate, and stripped of solvent by vacuum distillation. The residual brown oil was chromatographed on dry silica gel, using 1% ethanol in chloroform as developing solvent. Upon evaporation of the solvent and recrystallization of the residue from ether, 17-hydroxy-7 α -isopropoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone melting at 181—183°C. and further characterized by a specific rotation of +16.12° was obtained.

EXAMPLE 15

To a solution of 221 parts of 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone and 50 parts of 4-methylmorpholine in 2250 parts of tetrahydrofuran at -10°C. under nitrogen was added, with stirring, 65 parts of isobutyl chloroformate. A white precipitate formed immediately. Stirring was continued for 10 minutes, whereupon the reaction mixture was filtered; and the filtrate was stripped of solvent by vacuum distillation. The residual yellow oil, on chilling overnight, crystallized. The material thus isolated was the anhydride of 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone with isobutoxyformic acid which, recrystallized from hexane, melts at 144—146°C.

A solution of 49 parts of the anhydride of 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone with isobutoxyformic acid in 800 parts of isobutyl alcohol was heated at 90—95°C. under nitrogen for 12 hours. Solvent was removed by vacuum distillation, whereupon the residue crystallized. Recrystallization from methanol afforded 17-hydroxy-7 α -isobutoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone melting at 200—202°C. and having a specific rotation in chloroform solution of +17.40°.

Substitution of an equivalent quantity of methanol or of ethanol in the procedure of the preceding paragraph afforded, respectively, 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone, melting at 190—192°C.; and 7 α -ethoxycarbonyl-17-hydroxy-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone, melting at 143—145°C.

EXAMPLE 16

To a solution of 80 parts of 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone and 20 parts of 4-methylmorpholine in 600 parts of tetrahydrofuran at -15°C. under nitrogen was added, with stirring, 28 parts of isobutyl chloroformate. Precipitation occurred. Stirring was continued for 5 minutes, whereupon 640 parts of 2-propanol was introduced. The resultant mixture was filtered under nitrogen, and the filtrate was stripped of solvent by vacuum distillation. The residue was taken up in 1560 parts of 4-methyl-1-pentanol, and this solution was heated at the boiling point under reflux for 3 hours. Approximately 2000 parts of water was added at this point and boiling under reflux was then resumed for a further 35 hours. Solvent was thereupon removed by vacuum distillation, and the residue was extracted with ethyl acetate. The ethyl acetate extract was consecutively washed with aqueous 5% potassium bicarbonate and water, dried over sodium sulfate and magnesium sulfate, and finally stripped of solvent by vacuum distillation. The residue was chromatographed on dry silica gel, using 3 1/2% ethyl acetate in chloroform as developing solvent. On evaporation of solvent and recrystallization of the residue from ether, colorless crystalline 17-hydroxy-7 α -isohexyloxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone melting at 118—120°C. and with a specific rotation of +20.90° was obtained.

EXAMPLE 17

To a solution of 200 parts of 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone in 7000 parts of methanol under nitrogen was added, with stirring, 397 parts of aqueous 5% sodium hydroxide. The resultant mixture was stirred at 40°C. for 2 hours, then stripped of solvent by vacuum distillation. The residue was washed by slurrying with ethyl acetate and dried in air. The product thus isolated was sodium 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylate.

EXAMPLE 18

A mixture of 200 parts of 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid, 19 parts of calcium hydroxide, and 4000 parts of methanol was stirred at 40°C. under nitrogen for 2 hours. Solvent was then removed by vacuum distillation, and the residue was recrystallized from ethyl acetate. The product thus isolated was calcium bis[17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylate].

EXAMPLE 19

To 20 parts of 2-propanol, saturated with ammonia, was added 1 part of 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid. The resulting mixture was allowed to stand at room temperature for 24 hours, at which point solvent was removed by vacuum distillation. The residue was washed with ethyl acetate and dried in air. The product thus isolated was ammonium 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylate.

Similarly prepared from 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone monohydrate was ammonium 21-carboxy-17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α -carboxylate γ -lactone.

EXAMPLE 20

A mixture of 100 parts of 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone monohydrate, 9 parts of calcium hydroxide, and 5000 parts of 2-propanol was stirred at 40°C. under nitrogen for 2 hours. The resultant mixture was stripped of solvent by vacuum distillation, and the residue was slurried with hot ethyl acetate. The insoluble solids isolated by filtration were calcium bis[21-carboxy-17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α -carboxylate γ -lactone].

EXAMPLE 21

Substitution of an equivalent quantity of 7 α -ethoxycarbonyl-17-hydroxy-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone in the procedure of Example 9 afforded 7 α -ethoxycarbonyl-17-hydroxy-3-oxo-17 α -pregna-1,4-diene-21-carboxylic acid γ -lactone.

Similarly prepared from 17-hydroxy-7 α -isopropoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone was 17-hydroxy-7 α -isopropoxycarbonyl-3-oxo-17 α -pregna-1,4-diene-21-carboxylic acid γ -lactone.

EXAMPLE 22

A solution of 43 parts of 17-hydroxy-7 α -isopropoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone and 130 parts by volume of 0.73 *N* aqueous potassium hydroxide solution in approximately 785 parts of 2-propanol was allowed to stand at room temperature overnight, then was warmed at 50–55°C. for 20 minutes on a steam bath. The reaction mixture was cooled, concentrated *in vacuo* and washed with ethyl ether to afford, as a light yellow solid, potassium 17-hydroxy-7 α -isopropoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylate.

The above procedure was repeated using 7 α -ethoxycarbonyl-17-hydroxy-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone as the starting material and ethanol as the reaction solvent. The crude product was washed with ethyl acetate and ethyl ether, affording potassium 7 α -ethoxycarbonyl-17-hydroxy-3-oxo-17 α -pregn-4-ene-21-carboxylate monohydrate. That product is characterized by a specific rotation of +4.89° in water.

Similarly prepared from 7 α -ethoxycarbonyl-17-hydroxy-3-oxo-17 α -pregna-1,4-diene-21-carboxylic acid γ -lactone, 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregna-1,4-diene-21-carboxylic acid γ -lactone and 17-hydroxy-7 α -isopropoxycarbonyl-3-oxo-17 α -pregna-1,4-diene-21-carboxylic acid γ -lactone were potassium 7 α -ethoxycarbonyl-17-hydroxy-3-oxo-17 α -pregna-1,4-diene-21-carboxylate, potassium 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregna-1,4-diene-21-carboxylate and potassium 17-hydroxy-7 α -isopropoxycarbonyl-3-oxo-17 α -pregna-1,4-diene-21-carboxylate, respectively.

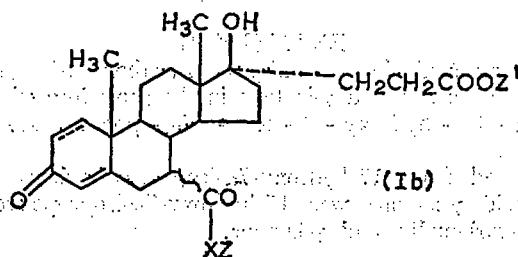
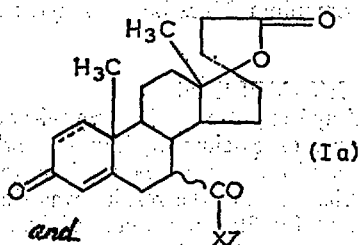
EXAMPLE 23

A solution of 10.0 parts of 4 α ,7 α -carbonyl-5-cyano-17-hydroxy-3-oxo-5 β ,17 α -pregnane-21-carboxylic acid γ -lactone and 5.4 parts of potassium hydroxide in approximately 240 parts of dry methanol was refluxed for 29 hours. The reaction mixture was then stripped of methanol *in vacuo* and the viscous yellow residue was dissolved in water. The aqueous solution thus obtained was acidified with 2 *N* hydrochloric acid

and the gummy precipitate which formed was extracted twice with ethyl acetate. The organic layer was extracted with saturated aqueous sodium chloride solution, then dried over magnesium sulfate and sodium sulfate. The ethyl acetate was removed *in vacuo*. The resultant yellow gum was heated with 200 parts by volume of 5% aqueous potassium hydroxide solution in 300 parts of methanol at the reflux temperature for 18 hours. Methanol was then removed *in vacuo*. The aqueous solution which remained was diluted with one volume of acetone, acidified with 2 N hydrochloric acid, and then allowed to stand at room temperature for 20 minutes. The acetone was thereupon removed *in vacuo*, affording a gummy mixture which was extracted twice with ethyl acetate. The organic layer was extracted several times with 5% aqueous potassium bicarbonate solution. Acidification of that basic solution, followed by filtration and drying of the resultant precipitate, afforded hydrated 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone, identical to that obtained in Example 4.

WHAT WE CLAIM IS:—

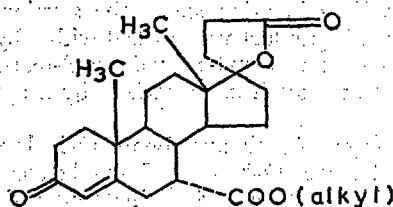
1. Compounds of the general formulae



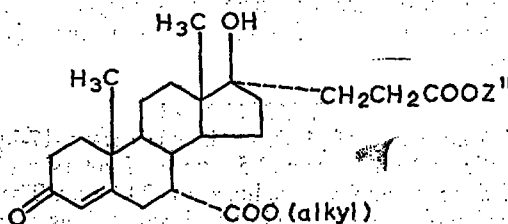
wherein Z is hydrogen, alkali metal, alkaline-earth metal/2, ammonium or alkyl; Z' is hydrogen, alkali metal, alkaline-earth metal/2 or ammonium when Z is alkyl; Z' is identical to Z when Z is hydrogen, alkali metal, alkaline-earth metal/2, or ammonium; the dotted line indicates the optional presence of a Δ^1 unsaturated linkage; the wavy line indicates the alternative α and β configurations; and X is oxygen, with the proviso that when Z is alkyl and the 1,2-linkage is saturated, X in formula (Ia) can also be sulfur.

2. 17-Hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone.

3. Compounds of the general formulae



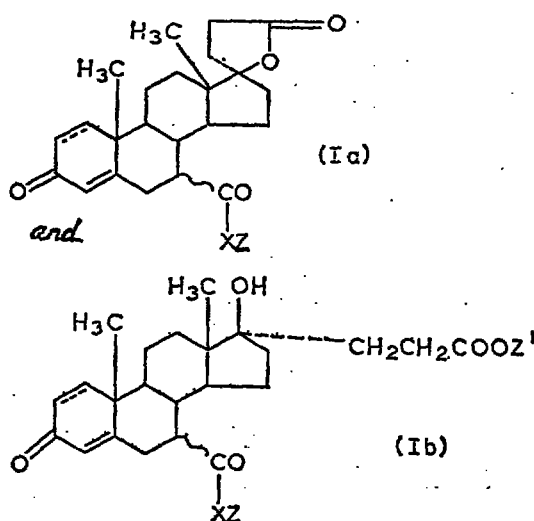
and



and the gummy precipitate which formed was extracted twice with ethyl acetate. The organic layer was extracted with saturated aqueous sodium chloride solution, then dried over magnesium sulfate and sodium sulfate. The ethyl acetate was removed *in vacuo*. The resultant yellow gum was heated with 200 parts by volume of 5% aqueous potassium hydroxide solution in 300 parts of methanol at the reflux temperature for 18 hours. Methanol was then removed *in vacuo*. The aqueous solution which remained was diluted with one volume of acetone, acidified with 2 N hydrochloric acid, and then allowed to stand at room temperature for 20 minutes. The acetone was thereupon removed *in vacuo*, affording a gummy mixture which was extracted twice with ethyl acetate. The organic layer was extracted several times with 5% aqueous potassium bicarbonate solution. Acidification of that basic solution, followed by filtration and drying of the resultant precipitate, afforded hydrated 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone, identical to that obtained in Example 4.

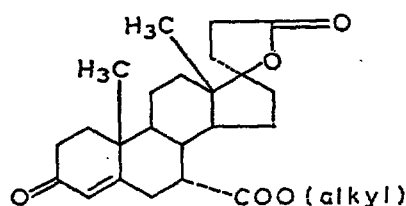
WHAT WE CLAIM IS:—

1. Compounds of the general formulae

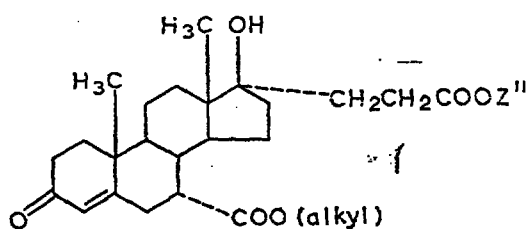


wherein Z is hydrogen, alkali metal, alkaline-earth metal/2, ammonium or alkyl; Z' is hydrogen, alkali metal, alkaline-earth metal/2 or ammonium when Z is alkyl; Z' is identical to Z when Z is hydrogen, alkali metal, alkaline-earth metal/2, or ammonium; the dotted line indicates the optional presence of a Δ^1 unsaturated linkage; the wavy line indicates the alternative α and β configurations; and X is oxygen, with the proviso that when Z is alkyl and the 1,2-linkage is saturated, X in formula (Ia) can also be sulfur.

2. 17-Hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone.
3. Compounds of the general formulae



and





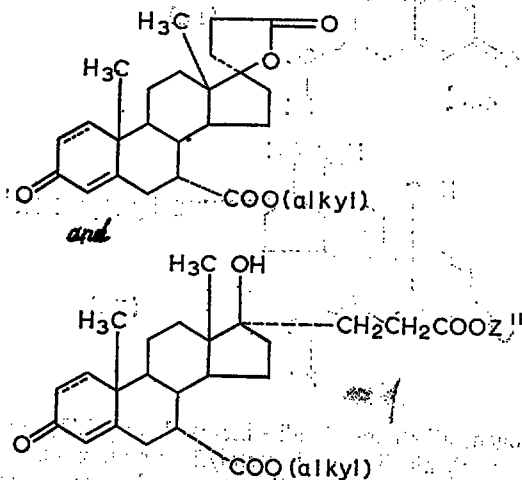
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wherein Z'' is alkali metal or alkaline-earth metal/2; and the dotted line indicates the optional presence of a Δ^1 unsaturated linkage.

4. Compounds of the general formulae



wherein Z'' is alkali metal or alkaline-earth metal/2.

5. 7α - Ethoxycarbonyl - 17 - hydroxy - 3 - oxo - 17α - pregn - 4 - ene - 21 - carboxylic acid γ -lactone.

10 6. 17 - Hydroxy - 7α - methoxycarbonyl - 3 - oxo - 17α - pregn - 4 - ene - 21 - carboxylic acid γ -lactone.

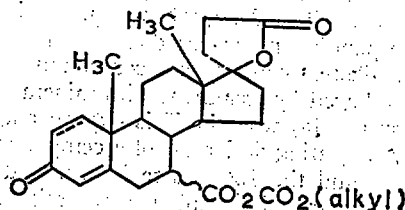
11 7. 17 - Hydroxy - 7α - isopropoxycarbonyl - 3 - oxo - 17α - pregn - 4 - ene - 21 - carboxylic acid γ -lactone.

15 8. Potassium 17-hydroxy- 7α -methoxycarbonyl-3-oxo- 17α -pregn-4-ene-21-carboxylate.

15 9. Potassium 17 - hydroxy - 7α - isopropoxycarbonyl - 3 - oxo - 17α - pregn - 4 - ene-21-carboxylate.

OS 10. Potassium 7α - ethoxycarbonyl - 17 - hydroxy - 3 - oxo - 17α - pregn - 4 - ene-21-carboxylate.

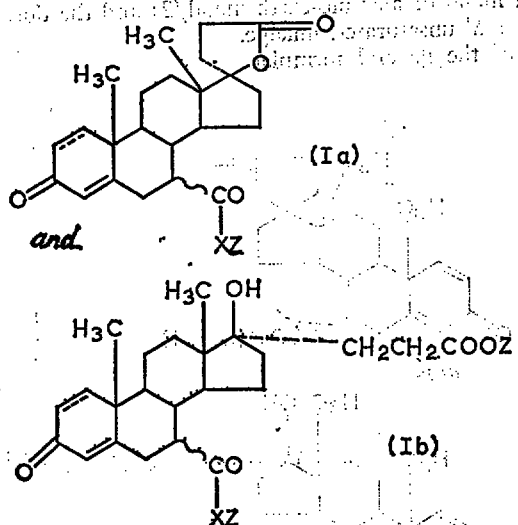
20 11. A compound of the general formula



wherein the dotted line indicates the optional presence of a Δ^1 unsaturated linkage; and the wavy line indicates the alternative α and β configurations.

25 12. The anhydride of 17-hydroxy-3-oxo- 17α -pregn-4-ene- 7α ,21-dicarboxylic acid γ -lactone with isobutoxyformic acid.

13. A process for the preparation of compounds of the general formulae.



wherein Z is hydrogen, alkali metal, alkaline-earth metal/2, ammonium or alkyl; Z' is hydrogen, alkali metal, alkaline-earth metal/2 or ammonium when Z is alkyl; Z' is identical to Z when Z is hydrogen, alkali metal, alkaline-earth metal/2 or ammonium; the dotted line indicates the optional presence of a Δ^1 unsaturated linkage; the wavy line indicates the alternative α and β configurations; and X is oxygen, with the proviso that when Z is alkyl and the 1,2-linkage is saturated, X in formula (Ia) can also be sulfur; which comprises a process selected from the group consisting of:

(a) contacting 4 α ,7 α - carbonyl - 5 - cyano - 17 - hydroxy - 3 - oxo - 5 β ,17 α - pregnane-21-carboxylic acid γ -lactone with an alkali metal alkoxide, to afford a mixture of the corresponding 7 α and 7 β compounds of formula (Ia) wherein X is oxygen, Z is alkyl and the 1,2-linkage is saturated, followed by isolation of the desired 7 α or 7 β isomer;

(b) contacting an active acylating derivative of a compound of formula (Ia) wherein X is oxygen and Z is hydrogen with an alkanol, to afford the corresponding compound of formula (Ia) wherein X is oxygen and Z is alkyl;

(c) dehydrogenating a compound of formula (Ia) wherein X is oxygen, Z is alkyl and the 1,2-linkage is saturated, to afford the corresponding compound of formula (Ia) wherein X is oxygen, Z is alkyl and the 1,2-linkage is unsaturated;

(d) reacting a compound of formula (Ia) wherein X is oxygen and Z is alkyl or hydrogen with, respectively, one or two equivalents of an appropriate base, in an aqueous medium, to afford the corresponding mono- or bis-(alkali metal) or (alkaline-earth metal/2) salt of formula (Ib); followed by, when required, brief exposure to a proton source, to afford the corresponding mono- or dicarboxylic acid of formula (Ib);

(e) hydrolysing under alkaline conditions a compound of formula (Ia) wherein X is oxygen and Z is alkyl, followed by treatment with mineral acid to afford the corresponding compound of formula (Ia) wherein X is oxygen and Z is hydrogen;

(f) contacting an active acylating derivative of a compound of formula (Ia) wherein X is oxygen, Z is hydrogen and the 1,2-linkage is saturated with an alkane-thiol, to afford the corresponding compound of formula (Ia) wherein X is sulfur, Z is alkyl and the 1,2-linkage is saturated;

(g) contacting 4 α ,7 α - carbonyl - 5 - cyano - 17 - hydroxy - 3 - oxo - 5 β ,17 α - pregnane-21-carboxylic acid γ -lactone with potassium hydroxide in methanol, followed by alkaline hydrolysis and subsequent treatment with mineral acid to afford the corresponding 7 α compound of formula (Ia) wherein X is oxygen, Z is hydrogen and the 1,2-linkage is saturated;

(h) contacting a compound of formula (Ia) or (Ib) wherein X is oxygen, Z is hydrogen or alkyl and Z' is hydrogen, Z and Z' being selected so that the molecule contains at least one acid hydrogen, with a quantity of an appropriate base equivalent to the amount of acid hydrogen present, in an aqueous medium, to afford the corresponding mono- or bis-(alkali metal) or (alkaline-earth metal/2) salt of formula (Ia) or (Ib); and

(i) contacting a compound of formula (Ia) wherein X is oxygen and Z is hydrogen or a compound of formula (Ib) wherein X is oxygen, Z is hydrogen or alkyl and Z' is hydrogen, with excess ammonia, to afford the corresponding compound of formula (Ia)



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wherein X is oxygen and Z is ammonium or of (Ib) wherein X is oxygen, Z is ammonium or alkyl and Z' is ammonium, respectively.

14. A process according to Claim 13(b) wherein the active acrylating intermediate is the anhydride of 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone with an alkoxyformic acid.

15. A process according to Claim 13(c) wherein the dehydrogenation is effected by use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

16. A process according to Claim 13(d) wherein the base is potassium hydroxide.

17. A process for the preparation of 17-hydroxy-7 α -methoxycarbonyl-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone which comprises contacting 4 α ,7 α -carbonyl-5-cyano-17-hydroxy-3-oxo-5 β ,17 α -pregnane-21-carboxylic acid γ -lactone with an alkali metal methoxide, followed by isolation of the desired 7 α isomer.

18. A process for the preparation of a 7 α -alkoxycarbonyl-17-hydroxy-3-oxo-17 α -pregn-4-ene-21-carboxylic acid γ -lactone wherein the alkoxy group is ethoxy, methoxy or isopropoxy, which comprises contacting ethanol, methanol or 2-propanol, respectively, with the mixed anhydride of an alkoxyformic acid and 17-hydroxy-3-oxo-17 α -pregn-4-ene-7 α ,21-dicarboxylic acid γ -lactone.

ELKINGTON & FIFE.

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