United States Patent Office 2,888,457 Patented May 26, 1959

2,888,457

BISMETHYLENEDIOXY STEROIDS AND METHODS OF MAKING SAME

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No Drawing. Application August 18, 1958 Serial No. 755,403

31 Claims. (Cl. 260—239.55)

This invention relates generally to new compounds derived from steroids which have attached to the condensed ring nucleus a dihydroxyacetone side chain. More particularly it is concerned with new steriods in which a dihydroxyacetone side chain of a pregnane or unsaturated pregnane is deactivated by formation of a bismethylenedioxy derivative. It is further concerned with a method for making such new compounds from steriods having a free or esterified dihydroxyacetone side chain.

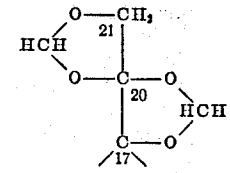
This application is a continuation-in-part of our copending application Serial No. 632,010, filed January 2, 1957, now abandoned.

It is well known that the vast majority of physiologically-active steroids are members of the pregnane series having a free or esterified dihydroxyacetone side chain at the C–17 position. This side chain is subject to oxidation at C–21, to reduction at C–20, to rearrangement leading to a D-homo steroid and to decomposition under strongly acidic or basic conditions. Since such reactions and reaction conditions are often necessary to modify or introduce functional substituents in the nucleus of the steroid molecule, the ability to deactivate or "block" the dihydroxyacetone side chain is important for the practical synthesis of physiologically-active steroids. Some success has been achieved by forming C–20 ethylenedioxy steroids but this blocking group is not completely satisfactory since it is quite acid labile and serves to deactivate only one portion of the dihydroxyacetone side chain, the ketone function.

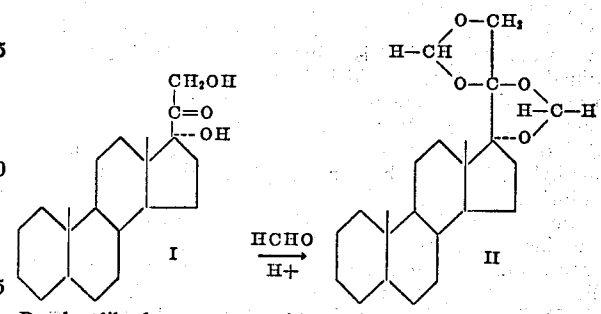
It is an object of our invention to provide a new series of steroid compounds in which the dihydroxyacetone side chain of a pregnane or unsaturated pregnane is deactivated by a very stable group wherein all three of the carbon atoms in the dihydroxyacetone chain are protected. It is a further object to protect the side chain of 17α,21-dihydroxy-20-keto pregnanes and unsaturated derivatives thereof with a group that can be conveniently removed to regenerate the dihydroxyacetone moiety. A more specific object is to provide new derivatives of steroids having a dihydroxyacetone side chain in which this functional moiety is protected by a bismethylenedioxy group. An additional object is a process for making this new type of steroid from a steroid having the dihydroxyacetone side chain. Other and further objects will become evident from the detailed explanation of our invention hereinbelow.

We have found that when a steroid having a dihydroxyacetone side chain attached to the condensed ring steriod nucleus is treated with formaldehyde in the presence of a strong acid there is obtained a bismethylenedioxy steroid in which all three carbon atoms of the dihydroxyacetone moiety are a part of at least one of the five-membered rings thus formed. We have also found that the presence of nuclear substituents or nuclear double bonds do not interfere with or prevent the formation of such bismethylenedioxy compounds. Thus, when the dihydroxyacetone moiety is at the C–17 position of the

nucleus, a compound is obtained having at carbons 17, 20 and 21 the structure



The new process may then be pictured structurally as applied to a steroid of the pregnane series having a dihydroxyacetone side chain at C–17 as follows:



By the dihydroxyacetone side chain is meant the 17α-hydroxy-20-keto-21-hydroxy moiety of a steroid such as I. We refer to such new steroids as 17-20,20-21 bismethylenedioxy steroids. Although the dihydroxyacetone moiety must be unsubstituted in order to react as shown above, the steroid actually charged to the reaction mixture may, if desired for convenience sake, be esterified at either or both of the hydroxy groups since such ester groups are hydrolyzed under the reaction conditions.

It will be evident that a dihydroxyacetone side chain located at positions of the steroid condensed ring nucleus other than at C–17, e.g. at C–16, at C–17a in D-homo steroids, and at other positions in the nucleus may also be converted by treatment with formaldehyde under our reaction conditions to the corresponding bismethylenedioxy compounds. However, since the physiologically-active steriods known at the present time have this function at C–17, we will discuss primarily those compounds, which may be described as 17α,21-dihydroxy-20-keto steroids of the pregnane series.

17-20,20-21 bismethylenedioxy steroids of the pregnane series are prepared by treating a 17α,21-dihydroxy-20-keto steroid of the pregnane series with formaldehyde in the presence of a strong acid. An excess of formaldehyde is employed in order to obtain the optimum yield of bis-dioxy compound.

In making a 17-20,20-21 bismethylenedioxy steroid we are able to use pure formaldehyde itself, the readily available 40% aqueous formaldehyde solution (formalin) or other compounds which act as a source of formaldehyde in the reaction mixture. Paraformaldehyde, formal and trioxane are examples of compounds which act as a source of formaldehyde.

The reaction is carried out in the presence of a strong acid, such as hydrochloric, perchloric, hydrobromic, sulfuric, phosphoric and like acids. Acids which have a $-\log k$ of less than 2.25 are considered strong acids for our process and any of these may be employed. The $-\log k$ of a large number of organic and inorganic acids appear in Lange's Handbook of Chemistry, Handbook Publisher's, Inc., 8th ed., 1952, pp. 1229–1233. This and similar tables in other texts provide ready information as to the $-\log k$ values of different acids so that acids suitable for use in our invention may be determined readily. Lewis acids or formic acid may also be used as the acid catalyst in preparing 17-20,20-21 bismethyl-

enedioxy steroids although the —log *k* of formic acid is 3.75.

The reaction of a 17α,21-dihydroxy-20-keto steroid with formaldehyde is carried out in an organic solvent inert under the reaction conditions. This may be a water-miscible solvent such as dioxane or tetrahydrofuran in which case the reaction takes place in a one-phase solvent system. Alternatively, and preferably formation of the 17-20,20-21 bismethylenedioxy steroid is effected in a two-phase reaction mixture wherein the steroid is dissolved in a water-immiscible organic solvent and the second phase is the aqueous acid-formaldehyde phase. Such an aqueous:organic solvent two-phase reaction mixture is very satisfactory and is preferred for optimum yields under our operating conditions. It is desirable that both the starting material and the reaction product be soluble in the organic solvent, but satisfactory yields and quality of 17-20,20-21 bismethylenedioxy steroids are obtained when the end product is soluble and the starting 17α,21-dihydroxy-20-keto-steroid is insoluble in the organic solvent. Suitable water-immiscible organic solvents for our process are chloroform, methylene chloride, ethylene dichloride, carbon tetrachloride, ethylene dibromide, methylene bromide, benzene, ethyl ether and the like, the chlorinated solvents being most satisfactory.

Formation of our new 17-20,20-21 bismethylenedioxy steroids of the pregnane series is ordinarily conducted at temperatures from about −30° C. to about +50° C. For ease of operation temperature of 0° C. to about +35° C. are preferred and satisfactory yields are realized at such temperatures with most steroids.

The time required for obtaining optimum yields of 17-20,20-21 bismethylenedioxy steroids will depend to some extent on the particular reaction temperature utilized. We have also found that the reaction time necessary for good yields is a function of the type of 17α,21-dihydroxy-20-keto steroid employed as starting material. For instance, in a chloroform-formalin-hydrochloric acid reaction system, about 40–50 hours are required for optimum conversion of cortisone to 17-20,20-21 bismethylenedioxy-4-pregnene-3,11-dione, whereas only 15–30 minutes are needed to convert prednisolone in high yield to 17-20,20-21 bismethylenedioxy-1,4-pregnadiene-11β-ol-3-one.

This difference in steroid reactivity does not, however, present any serious difficulty in readily determining the proper length of time to run the reaction under any desired process condition. The course of conversion of the 17α,21-dihydroxy-20-keto moiety of a steroid of the pregnane series to a 17-20,20-21 bismethylenedioxy derivative is readily followed by use of the dianisole bisdiphenyltetrazolium chloride reagent, commonly known as the B.T. reagent. This reagent reacts with a dihydroxyacetone grouping of a steroid to give a deep blue solution. It does not form a blue color with the 17-20,20-21 bismethylenedioxy steroids. By means of this B.T. test, therefore, the degree of reaction can be followed quantitatively, or if desired only semi-quantitatively, since the intensity of the blue color is a function of the amount of 17α,21-dihydroxy-20-keto steroid present in the solution tested. This intensity of color can conveniently be measured against a known standard solution and the extent of reaction easily calculated. Use of the Blue Tetrazolium (B.T.) reagent in assaying for the presence of a dihydroxyacetone moiety is described more fully in a publication by Mader et al., Anal. Chem. 24, 666 (1952).

By the process discussed above, and where necessary following the course of reaction by the B.T. test, any 17α,21-dihydroxy-20-keto steroid of the pregnane series may be converted to a 17-20,20-21 bismethylenedioxy steroid.

Functional groups or substituents in other parts of the pregnane molecule do not interfere with formation of the bismethylenedioxy side chain and in most cases are not

themselves destroyed or modified under the reaction conditions. Since strong acid is present during the reaction, any unusually acid-sensitive substituents in other portions of the molecule might possibly react and we prefer, where such side reactions are undesired and apt to occur, to temporarily form, if feasible, an acid stable derivative of such substituents. In the case of 11-hydroxylated steroids, reaction at the 11-position may be substantially eliminated by carrying out our process in a solvent system essentially free of alcohols, particularly the lower alkanols. Thus, in an alcohol free system, hydrocortisone and prednisolone are readily converted by treatment with formaldehyde and strong acid to 17-20,20-21 bismethylenedioxy-4-pregnene-11β-ol-3-one and 17-20,20-21 bismethylenedioxy-1,4-pregnadiene-11β-ol-3-one respectively. If alcohol should be present the 17-20,20-21 bismethylenedioxy derivative, of course, forms but an alkoxymethyl ether derivative of the 11-hydroxy group is also formed. This is, however, cleaved during removal of the bismethylenedioxy function.

Where functional substituents in other parts of the molecule, such as amines, are those that normally react with aldehydes, they will react during our process. This is not a serious difficulty since in most instances the original functional group can be regenerated readily.

We are able, therefore, to carry out our new process on steroids of the pregnane series generally. Ordinarily the steroid reactants will be substituted at the 3-position with an oxygen-containing function or a function reconvertible by hydrolysis to an oxygenated group, such as a keto or hydroxy group, or an ethylenedioxy, enamine, enol ether, or ester moiety. The steroids may also have substituents such as hydroxy, keto, halo, ether or lower alkyl groups at other positions of the condensed ring nucleus, as for instance at positions 1, 2, 3, 4, 6, 7, 9, 11, 12, 14, 15 or 16. A preferred group of 17-20,20-21 bismethylenedioxy steroids of the invention have oxygenated functions at both the 3 and 11 positions of the condensed ring system. Also included within the preferred embodiments of the invention are those bismethylenedioxy steroids having a halogen group, such as chloro, bromo or fluoro, at the 9-position of the ring. Our new compounds may be completely saturated or have one or more double bonds attached, for example, to carbon atoms 1, 4, 5, 6, 7, 11 or 14. For example, there may be double bonds in the 1:2, 4:5, 5:6, 8:9, 9:11 and at other positions of the molecule. Some representative examples of new steroids made by the method of our invention from the corresponding 17α,21-dihydroxy-20-keto steroids are—

17-20,20-21 bismethylenedioxy-pregnan-3-ol
17-20,20-21 bismethylenedioxy-4-pregnen-3-one
17-20,20-21 bismethylenedioxy-4-pregnene-3,11-dione
17-20,20-21 bismethylenedioxy-1,4-pregnadiene-3,11-dione
17-20,20-21 bismethylenedioxy-1,4-pregnadiene-11β-ol-3-one
17-20,20-21 bismethylenedioxy-9α-fluoro-1,4-pregnadiene-11β-ol-3-one
17-20,20-21 bismethylenedioxy-12α-fluoro - 1,4 - pregnadiene-3,11-dione
17-20,20-21 - bismethylenedioxy - 6 - methyl-1,4-pregnadiene-11β-ol-3-one
17-20,20-21 bismethylenedioxy-12α-chloro - 4 - pregnene-11β-ol-3-one
17-20,20-21 bismethylenedioxy - 4,6 - pregnadiene - 3,11-dione
17-20,20-21 bismethylenedioxy-9α-fluoro-4-pregnene-11β-ol-3-one
17-20,20-21 bismethylenedioxy - 4 - pregnen-9α,11β-diol-3-one
17-20,20-21 bismethylenedioxy-allopregnane-3,11-dione
17-20,20-21 bismethylenedioxy-19-nor-4-pregnene-11β-ol-3-one
17-20,20-21 bismethylenedioxy-4-pregnen-6-ol-3-one
17-20,20-21 bismethylenedioxy-4,9(11)-pregnadien-3-one

17-20,20-21 bismethylenedioxy - 9α - chloro-4-pregnene-11β-ol-3-one

17-20,20-21 bismethylenedioxy - 16 - methyl-1,4-pregnadiene-11β-ol-3-one

17-20,20-21 bismethylenedioxy-4-pregnene-11β-ol-3-one

17-20,20-21 bismethylenedioxy - 9α - fluoro-16-methyl-1,4-pregnadiene-11β-ol-3-one

17-20,20-21 bismethylenedioxy-4-chloro-pregnane-3,11-dione

17-20,20-21 bismethylenedioxy-4,8(9)-pregnadien-3-one

The desired products are isolated from the reaction mixture by extraction into an organic solvent followed by a chromatographic separation or by recrystallization from a suitable solvent. Certain of the 3,11-bisoxygenated-17-20,20-21 bismethylenedioxy ring A unsaturated steroids of the pregnane series have cortisone-like activity and may themselves be used in the treatment of diseases which respond to anti-inflammatory agents. For the most part, however, the greatest value of our new compounds lies in the fact that they represent intermediates in which the important C–17 dihydroxyacetone side chain is rendered chemically inert and inaccessible so that reactions and transformations which would destroy an unprotected dihydroxyacetone moiety may be used safely on other portions of the steroid molecule. For example, Claisen condensations at positions alpha to a carbonyl group may be carried out without undesirable reaction in the side chain. In this way 2-methyl cortisone or 2-methylhydrocortisone may be prepared from cortisone or hydrocortisone by first making the 17-20,20-21 bismethylenedioxy derivative, treating the resulting compound successively with methyl oxalate and a methylating agent, and finally treating the 2-methyl-17-20,20-21 bismethylenedioxy steroid with sulfuric acid to reverse the bismethylenedioxy function and obtain the 2-methyl cortisone or hydrocortisone. This process would not be feasible with an unprotected dihydroxyacetone side chain since extensive side reaction would occur at the 21-position.

Furthermore, after inactivation of the side chain by our method, it is now possible to treat a 17α,21-diol-20-keto steroid of the pregnane series having a nuclear carbonyl or oxide function with a metal alkyl or metal Grignard reagent thereby alkylating the nucleus without adverse reactions in the side chain. These new compounds also provide a convenient method for selectively reducing a carbonyl group in the A ring of the steroid nucleus without also reducing the 20-keto substituent, and for selectively blocking, for any purpose, the 20-keto substituent of a 3,20-diketo steroid.

When the desired reactions have been performed on the steroid with the protected dihydroxyacetone side chain, the side chain can be readily regenerated by treatment of the 17-20,20-21 bismethylenedioxy compound with acid. This process of reforming the 17α,21-dihydroxy-20-keto steroid of the pregnane series is more fully described in our copending application Serial No. 632,026, filed January 2, 1957.

The following examples are given for purposes of illustration and not by way of limitation:

EXAMPLE 1

17-20,20-21 bismethylenedioxy-4-pregnene-3,11-dione

500 mg. of cortisone is suspended in 40 ml. of chloroform and 10 ml. of formalin (40% aqueous formaldehyde) and 10 ml. of concentrated hydrochloric acid are added. This two-phase system is stirred vigorously at room temperature for 52 hours. The aqueous phase is then made alkaline with aqueous sodium hydroxide, separated and extracted twice with chloroform. After washing with sodium bisulfite solution the chloroform is evaporated to give 685 mg. of crystalline residue. After recrystallization from acetone and methanol, 17-20,20-21 bismethylenedioxy-4-pregnene-3,11-dione of melting point 253–259° C. is obtained. Further purfication raises the melting point to 259–262° C.

EXAMPLE 2

17-20,20-21-bismethylenedioxy-4-pregnene-3,11-dione

500 mg. of cortisone free alcohol is suspended in 25 ml. of chloroform. To this mixture is added a solution of 10 ml. of concentrated hydrochloric acid and 10 ml. of formalin. The two-phase reaction mixture is stirred at room temperature for 19 hours, and at the end of this time, the chloroform layer is separated. It is washed with a saturated solution of sodium bicarbonate, dried and concentrated under vacuum to an amorphous residue. Upon treament with boiling methanol, a crystalline product separates weighing 328 mg. and having a melting point of 220–247° C. Further recrystallization from acetone-methylene chloride yields substantially pure 17-20,20-21-bismethylenedioxy-4-pregnene-3,11-dione.

The same product is obtained when a methylene chloride solution of cortisone is heated with formalin and perchloric acid under the conditions described above.

EXAMPLE 3

17-20,20-21-bismethylenedioxy-4-pregnene-3,11-dione

To a solution of 500 mg. of cortisone acetate in 25 ml. of chloroform is added a mixture of 10 ml. of formalin and 10 ml. concentrated hydrochloric acid. This two-phase reaction mixture is stirred at room temperature for 70 hours. At the end of this time, the chloroform layer is separated and the inorganic layer extracted with chloroform. This chloroform extract is added to the original chloroform layer and the solution washed with dilute soduim bisulfate, then dried over magnesium sulfate. The chloroform is removed under reduced pressure and an amorphous gum obtained, weighing 475 mg. After purification by chromatographing on acid washed alumina and elution with ether 180 mg. of 17-20,20-21-bismethylenedioxy-4-pregnene-3,11-dione is obtained.

In like manner 4,9(11)-pregnadien-17α,21-diol-3,20-dione is converted to 17-20,20-21-bismethylenedioxy-4,9(11)-pregnadien-3-one, and 4-pregnen-17α,21-diol-3,20-dione 21-acetate to 17-20,20-21-bismethylenedioxy-4-pregnen-3-one.

EXAMPLE 4

17-20,20-21-bismethylenedioxy-4-pregnene-11β-ol-3-one
17-20,20-21-bismethylenedioxy-4-pregnene-3,11-dione

To 500 mg. of hydrocortisone suspended in 25 ml. of chloroform is added a mixture of 10 ml. of formalin and 10 ml. of concentrated hydrochloric acid. The two-phase reaction mixture is stirred at room temperature for a period of 72 hours. At the end of this time, the layers are separated and the inorganic layer washed with chloroform. The combined chloroform extracts are washed with a saturated solution of sodium bicarbonate and then dried and concentrated under reduced pressure. The resulting gum is chromatogramed on acid washed alumina and washed alumina and a non-crystalline product obtained which is negative in the B.T. test and has the infrared spectrum expected for 17-20,20-21-bismethylenedioxy-4-pregnene-11β-ol-3-one.

This non-crystalline material is dissolved in 2 ml. of acetic acid and to this solution is added 60 mg. of chromium trioxide. The reaction mixture is allowed to stand at room temperature for ten minutes and at the end of this time, 5 ml. of water added to the mixture. The mixture is extracted several times with methylene chloride, the methylene chloride extracts washed with dilute sodium bicarbonate, then dried and concentrated to yield 17-20,20-21-bismethylenedioxy-4-pregnene-3,11-dione.

EXAMPLE 5

17-20,20-21-bismethylenedioxy-1,4-pregnadiene-3,11-dione

To a suspension of 500 mg. of prednisone in 25 ml. of chloroform is added a mixture of 10 ml. of formalin

and 10 ml. of concentrated hydrochloric acid. The two-phase system is stirred at room temperature for 70 hours, and the two layers are then separated. The aqueous layer is extracted once with chloroform and the chloroform extract combined with the original organic solvent layer. The chloroform is washed with a saturated solution of sodium bicarbonate, dried and concentrated under reduced pressure to a semi-crystalline solid weighing 712 mg. This crude product is triturated with boiling methanol and 352 mg. of crystalline material obtained, melting point 175–195° C. After recrystallization of this material from acetone and methanol, a pure sample of 17-20,20-21-bismethylenedioxy - 1,4 - pregnadiene - 3,11-dione, melting point 214–217° C., is obtained.

The same product is obtained by using sulfuric acid in place of hydrochloric acid.

EXAMPLE 6

Preparation of 17-20,20-21-bismethylenedioxy-1,4-pregnadiene-11β-ol-3-one-11-methoxymethylether

To a suspension of 500 mg. of prednisolone in 25 ml. of chloroform is added a mixture of 10 ml. of formalin and 10 ml. of concentrated hydrochloric acid. This two-phase system is stirred at room temperature for a period of 45 hours. At the end of this time, the two layers are separated. The aqueous layer is extracted once with chloroform and the chloroform extract combined with the original organic phase. The combined chloroform solution is washed with a saturated solution of sodium bicarbonate, dried and concentrated under reduced pressure to a semi-crystalline solid weighing 500 mg. This product is recrystallized from methanol to yield 300 mg. of product, melting at 191–202° C. Recrystallization from acetone and methanol gives a pure sample of 17-20, 20-21 - bismethylene-dioxyl-1,4-pregnadiene - 11β - ol - 3-one-11-methoxymethylether, melting point 217–220° C.

EXAMPLE 7

17-20,20-21-bismethylenedioxy-4,6-pregnadiene-3,11-dione

A solution of 1.106 grams of 4,6-pregnadiene-3,11,20-trione-17α,21 diacetate in 50 ml. of anhydrous methanol is stirred in a nitrogen atmosphere for one-half hour. 2.5 ml. of a 2 N methanolic solution of sodium methoxide is added and stirring continued for five minutes. 0.3 ml. of water is then added and stirring continued for an additional five minutes, and the solution then acidified with acetic acid. The solvent is removed under reduced pressure, the residue dissolved in chloroform and the chloroform extracted in sequence with water, 10% sodium bicarbonate and finally with water. The chloroform solution is dried over sodium sulfate and the solvent removed under reduced pressure to give 1.09 grams of crude 4,6-pregnadien-17α,21-diol-3,11,20-trione.

A mixture of this diol, 50 ml. of chloroform, 20 ml. of concentrated hydrochloric acid and 20 ml. of formalin is stirred vigorously at room temperature for 64 hours. 50 ml. of chloroform and 50 ml. of water are then added, the layers separated, and the organic phase washed in sequence with water, 10% sodium bicarbonate and again with water. After drying with sodium sulfate, the chloroform is removed under reduced pressure to give a residue of 17 - 20,20 - 21 - bismethylenedioxy - 4,6 - pregnadiene-3,11-dione.

This product is dissolved in benzene, adsorbed on acid washed alumina and eluted with ether. Evaporation of the ether gives the desired compound which, when crystallized from methanol, has melting point 239–243° C. (dec.) and $[\alpha]_D^{25°}$ +119° (chloroform).

Following the reaction conditions described in paragraphs two and three above, and using benzene as the organic solvent and hydrobromic acid in place of hydrochloric acid, 17-20,20-21-bismethylenedioxy-6-methyl-9α-fluoro-1,4-pregnadiene-11β-ol-3-one is obtained from 6-methyl - 9α - fluoro - 1,4 - pregnadiene - 11β,17α,21 - triol-3,20-dione.

EXAMPLE 8

17 - 20,20 - 21 - bismethylenedioxy - 1,4 - pregnadiene-11β-ol-3-one

To a suspension of 500 mg. of 1,4-pregnadiene-11β-17α,21-triol-3,20-dione in 25 ml. of chloroform is added a mixture of 10 ml. of formalin and 10 ml. of concentrated hydrochloric acid. The reaction mixture is stirred vigorously at room temperature for one hour and at the end of this time, the chloroform layer is separated and washed with a saturated solution of sodium bicarbonate. It is dried and concentrated under reduced pressure to give a gum which crystallizes upon trituration with boiling methanol. This product is recrystallized several times from ethyl acetate to yield 17-20,20-21-bismethylenedioxy-1,4-pregnadiene-11β-ol-3-one.

EXAMPLE 9

17 - 20,20 - 21 - bismethylenedioxy - 9α - fluoro - 4 - pregnene-11β-ol-3-one

Five grams of 9α-fluorohydrocortisone acetate are dissolved in 250 ml. of chloroform. To the stirred solution is added 100 ml. of concentrated hydrochloric acid and 100 ml. of 37% aqueous formaldehyde (formalin). After stirring at room temperature for 18 hours, the chloroform layer is separated, washed with saturated sodium bicarbonate, dried and evaporated to dryness. Trituration of the oil with methanol gives 1.1 grams of 17-20,20-21-bismethylenedioxy - 9α - fluoro - 4 - pregnene - 11β -ol-3-one, melting point (245°) 248–255° C.

EXAMPLE 10

Twenty grams of 9α-fluorohydrocortisone alcohol are dissolved in one liter of chloroform and to this stirred solution is added 400 ml. of concentrated hydrochloric acid and 400 ml. of formalin. The reaction mixture is stirred at room temperature for one hour and worked up as described in Example 9. The product melts at 250–260° C., 285–290° C.

EXAMPLE 11

Hydrolysis and acetylation of 17-20,20-21-bismethylenedioxy-4-pregnene-3,11-dione to cortisone acetate

To 100 mg. of the bismethylenedioxy derivative obtained as in Example 1 is added 5 ml. of methanol and 5 ml. of 5 N sulfuric acid and the heterogeneous mixture refluxed on the steam bath for one hour (homogeneous after 45 minutes). The methanol is removed in vacuo and the resulting aqueous solution thoroughly extracted with ethyl acetate. The extract is washed with sodium bicarbonate, dried and concentrated to give 96 mg. of residue. This is dissolved in 0.3 ml. of pyridine and 0.3 ml. of acetic anhydride. The mixture is heated for ten minutes on the steam bath and poured into water. The resultant mixture is extracted several times with methylene chloride, the methylene chloride washed with dilute hydrochloric acid and sodium bicarbonate, dried over magnesium sulfate and evaporated. The residue is recrystallized from acetone to give cortisone acetate.

EXAMPLE 12

17-20,20-21-bismethylenedioxy-4-pregnene-11β-ol-3-one

30 grams of hydrocortisone are combined with 1500 ml. of chloroform and to this solution is added a cooled mixture of 600 ml. of concentrated hydrochloric acid and 600 ml. of formalin. The reaction mixture is stirred at room temperature for one hour. The two layers are separated, the aqueous layer extracted with chloroform and the solution combined. They are washed with sodium bisulfate, dried and concentrated in vacuo. The entire residue is chromatographed on acid washed alumina. Elution of the column with 1:4 petroleum ether-

ether yields four grams of crystalline 17-20,20-21-bismethylenedioxy - 4 - pregnene - 11β - ol - 3 - one - 11-methoxymethylether, melting point 160–165° C. From the ether eluate there is obtained ten grams of 17-20, 20-21-bismethylenedioxy-4-pregnene-11β-ol-3-one, melting point 217–222° C.

EXAMPLE 13

17-20,20-21-bismethylenedioxy-4-pregnene-11β-ol-3-one

Two grams of hydrocortisone are dissolved in 100 ml. of chloroform which had been shaken with sulfuric acid, dried over calcium chloride and distilled. To this mixture is added with cooling 60 ml. of concentrated hydrochloric acid and 60 ml. of methanol free 37% aqueous formaldehyde. The reaction mixture is stirred for eight hours at room temperature. Following the isolation procedure described in the previous examples, there is obtained crystalline 17-20,20-21-bismethylenedioxy-4-pregnene-11β-ol-3-one, melting point 200–220° C., upon trituration of the oil with ethylacetate.

EXAMPLE 14

17-20,20-21 bismethylenedioxy-9α-chloro-4-pregnene-11β-ol-3-one

Ten grams of 9,11β-oxido-4-pregnen-17α-21-diol-3,20-dione are suspended in 500 ml. of methylene chloride and to this mixture is added 20 ml. of hydrochloric acid and 20 ml. of formalin. The reaction is stirred at room temperature for 90 minutes. Isolation of the reaction product as described above yields seven grams of 17-20,20-21 bismethylenedioxy-9α-chloro-4-pregnene-11β - ol - 3 - one, melting point 180–190° C. Recrystallization from methylene chloride-methanol gives pure material, melting point 220–230° C.

EXAMPLE 15

17-20,20-21 bismethylenedioxy-1-pregnene-3,11-dione

A mixture of four grams of 1-pregnen-17α,21-diol-3,11,20-trione, 200 ml. of chloroform, 80 ml. of concentrated hydrochloric acid and 80 ml. of formalin is stirred vigorously at room temperature for 48 hours. At the end of this time the chloroform layer is separated and washed with three small portions of 5% potassium carbonate and then with water until the water washings are neutral. The chloroform solution is dried over magnesium sulfate and the solvent removed in vacuo. There is obtained a light yellow oily solid. On crystallization of this material from acetone and recrystallization from methylene chloride-methanol substantially pure 17-20,20-21 bismethylenedioxy - 1 - pregnene-3,11-dione, melting point 230–233° C., is obtained.

EXAMPLE 16

17-20,20-21 bismethylenedioxy-allopregnane-11β-ol-3-one

To a solution of 7.1 grams of allopregnane-11β,17α,21-triol-3,20-dione in 350 ml. of chloroform is added 140 ml. of cold concentrated hydrochloric acid and 140 ml. of cold neutral formalin. The two-phase mixture is stirred for two hours. The solvent layers are separated and the aqueous phase extracted with two 100 ml. portions of chloroform. The chloroform solutions are combined, washed successively with water, 5% sodium bicarbonate and water, and then dried over anhydrous magnesium sulfate. The chloroform is then removed in vacuo and the resulting residue chromatographed over 180 grams of alumina. Elution of the column with ethyl ether yields, after recrystallization from ether-petroleum ether, 17 - 20,20 - 21 bismethylenedioxy - allopregnane-11β-ol-3-one-11-methoxymethylether; further elution with ethyl ether gives 17-20,20-21 bismethylenedioxy-allopregnane-11β-ol-3-one, melting point 220–225° C., after recrystallization from ether.

Following the procedure set forth in the above paragraph and starting with 6.5 grams of 9α-fluoro-1,4-pregnadiene-11β,17α,21-triol-3,20-dione there is obtained 17-20,20-21 bismethylenedioxy-9α-fluoro-1,4-pregnadiene-11β-ol-3-one.

EXAMPLE 17

17-20,20-21 bismethylenedioxy-4-pregnan-3-one

500 mg. of 4-pregnen-17α,21-diol-3,20-dione in 25 ml. of chloroform is added to a mixture of 10 ml. of concentrated hydrochloric acid and 10 ml. of formalin. The resulting two-phase system is stirred at room temperature for 44 hours. At the end of which time the phases are separated and the aqueous phase extracted with two 25 ml. portions of chloroform. The chloroform extracts are combined, washed with aqueous sodium bicarbonate and with water, dried and finally distilled. The residual solid is washed with petroleum ether to give 327 mg. of 17-20,20-21 bismethylenedioxy-4-pregnen-3-one, melting point 220–245° C. Recrystallization from methanol and methylene chloride-ether raises the melting point to 250–255° C.

In a similar fashion by employing 4,9(11)-pregnadien-17α,21-diol-3,20-dione as the starting material and using sulfuric in place of hydrochloric acid, there is obtained 17 - 20,20-21 bismethylenedioxy-4,9(11)-pregnadien-3-one, melting point 218–222° C.

EXAMPLE 18

17-20,20-21 bismethylenedioxy-9α-chloro-4-pregnene-11β-ol-3-one

One gram of 9α-chloro hydrocortisone acetate in 100 ml. of methylene chloride is added to a pre-cooled mixture of 25 ml. of methanol free formaldehyde in 25 ml. of concentrated hydrochloric acid. The reaction mixture is stirred at room temperature for 18 hours. The methylene chloride layer is then separated and washed with water and a solution of saturated sodium bicarbonate. It is evaporated to dryness in vacuo after having been dried over magnesium sulfate. The resulting crystalline residue is recrystallized from methylene chloride-methanol to give 17-20,20-21 bismethylenedioxy-9α-chloro-4-pregnene-11β-ol-3-one, melting point 220–230° C.

Following the procedure set forth immediately above and using 98% formic acid in place of the hydrochloric acid, 17-20,20-21 bismethylenedioxy-16β-chloro-4-pregnene-3,11-dione is obtained from 16β-chloro cortisone.

EXAMPLE 19

17-20,20-21 bismethylenedioxy-9α-bromo-4-pregnene-11β-ol-3-one

To a stirred solution of 1.6 grams of 9,11-oxido-4-pregnen-17α,21-diol,3-20-dione in 100 ml. of chloroform is added a cold mixture of 50 ml. of formaldehyde and 50 ml. of 40–42% hydrobromic acid. The reaction mixture is stirred at room temperature for 4½ hours. At the end of this time the chloroform layer is separated, washed with water and sodium bicarbonate solution, and dried. The chloroform is then removed in vacuo and the residual oil triturated with methanol. Crystals of 17-20,20-21 bismethylenedioxy-9α-bromo-4-pregnene-11β-ol-3-one are obtained which, after recrystallization from methanolmethylene chloride, melts at 170–177° C.

Oxidation of this substance with pyridine-chromium trioxide complex yields 17-20,20-21 bismethylenedioxy-9α-bromo-4-pregnene-3,11-dione.

EXAMPLE 20

17-20,20-21 bismethylenedioxy-16α-methyl-4-pregnene-3,11-dione

24 grams of 16α-methyl cortisone is dissolved in 910 ml. of chloroform and to this solution is added with stirring 237 ml. of 37% hydrochloric acid and 237 ml. of 37% formaldehyde. This mixture is stirred at room temperature for 70 hours. The chloroform layer is then sep-

arated and the aqueous layer extracted twice with 50 ml. of chloroform. The chloroform solution and extracts are combined, washed with saturated sodium bicarbonate solution and with water. The chloroform solution is then dried over magnesium sulfate and concentrated in vacuo until crystallization occurs. The resulting slurry is flushed with 100 ml. of methanol to remove the chloroform and then dissolved in approximately 200 ml. of methanol. The methanol solution is concentrated in vacuo to a volume of about 75 ml. and cooled to 0–5° C. The slurry is filtered and the crystalline material washed with cold methanol to give 17-20,20-21 bismethylenedioxy-16α-methyl-4-pregnene-3,11-dione, melting point 231–236° C.

The same product is obtained when sulfurous acid is used in place of hydrochloric acid as the acid catalyst.

EXAMPLE 21

17-20,20-21 bismethylenedioxy-16α-methyl-4-pregnene-11β-ol-3-one

A mixture of 47.5 ml. of formaldehyde (low in methanol content) and 47.5 ml. of concentrated hydrochloric acid are added at 0° C. to a solution of 5 grams of 16α-methyl hydrocortisone in 182 ml. of methanol-free chloroform. The mixture is stirred at room temperature in a nitrogen atmosphere for 24 hours. The chloroform layer is then separated and the aqueous layer extracted with chloroform. The chloroform solutions are combined, washed with two 50 ml. portions of water, sodium bicarbonate solution and water. The chloroform solution is then dried over magnesium sulfate, filtered and concentrated to dryness. The residue is triturated with cold methanol and the crude solid thus obtained is dissolved in 215 ml. of benzene and chromatographed on 400 mg. of Florosil, elution with 10% acetone in n-hexane and concentration of these fractions yields 17-20,20-21 bismethylenedioxy-16α-methyl-4-pregnene-11β-ol-3-one, melting 278–283° C.

The 11β-methoxy methyl ether of said substance is obtained on elution of the column with 7% acetone in n-hexane, melting point 240–243° C. after recrystallization from chloroform-hexane.

EXAMPLE 22

(*a*) Following the procedure of Example 1 hereinabove treatment of 2α-methyl cortisone with formaldehyde in the presence of sulfuric acid yields 17-20,20-21 bismethylenedioxy-2α-methyl-4-pregnene-3,11-dione, melting point 248–258° C.; when 11α-methyl hydrocortisone is used as the starting material, there is obtained 17-20,20-21 bismethylenedioxy-11α-methyl-4-pregnene-11β-ol-3-one, melting point 203–212° C.

(*b*) On treatment of a chloroform solution of 6α-methyl hydrocortisone with 98% formic acid under the conditions of Example 7 hereinabove there is obtained 17-20,20-21 bismethylenedioxy-6α-methyl-4-pregnene-11β-ol-3-one, melting point 275–279° C. It is important that the reaction medium employed in making this substance be substantially methanol-free.

EXAMPLE 23

17-20,20-21 bismethylenedioxy-16β-methyl-4-pregnene-3,11-dione

To a stirred solution of 7.43 grams of 16β-methyl cortisone alcohol in 365 ml. of methylene chloride at room temperature is added a solution, premixed at 0° C., of 110 ml. of low-methanol content formaldehyde (37% aqueous solution) and 110 ml. of concentrated hydrochloric acid. The reaction mixture is stirred at room temperature for 20 hours, followed by addition of 960 ml. of water. The layers are separated and the aqueous layer extracted with three 200 ml. portions of methylene chloride. The combined methylene chloride layer and extracts are washed with 200 ml. of water and excess potassium bicarbonate, and two 200 ml. portions of water; they are dried over magnesium sulfate and taken to dryness in vacuo (flushed twice with benzene). The residue is triturated with ether to yield 6.69 grams of crystalline 17-20,20-21 bismethylenedioxy-16β-methyl-4-pregnene-3,11-dione, melting point 220–247° C. (dec.).

The starting material for making this material is prepared as follows:

To a solution of 3α-acetoxy-16-pregnene-11,20-dione in a mixture of tetrahydrofuran and ethyl ether is added diazomethane to produce 3α-acetoxy-16α,17α-methyleneazopregnane-11,20-dione (melting point 186–190° C.) which precipitated from solution. Heating this compound at about 180° C. in vacuo produces 3α-acetoxy-16-methyl-16-pregnene-11,20-dione (melting point 165–167° C.) which upon reaction with hydrogen peroxide in the presence of sodium hydroxide in methanol solution for 18 hours at room temperature affords 16α,17α-epoxy-3α-hydroxy-16β-methyl-pregnane-11,20-dione (melting point 178–180° C.). When this compound is treated with perchloric acid in aqueous dioxane at 25–30° C. for 65 hours and the resulting reaction mixture is diluted with water a mixture of 3α,17α-dihydroxy-16-methyl-15-pregnene-11,20-dione and 3α,17α-dihydroxy-16-methylene-pregnane (melting point 158–167° C.) is precipitated and recovered by filtration. Reduction of this mixture with hydrogen in methanol in the presence of palladium-calcium carbonate catalyst affords a mixture of 3α,17α-dihydroxy-16α-methylpregnane-11,20-dione and 3α,17α-dihydroxy-16β-methylpregnane-11,20-dione sintering at 150° C. Bromination of this mixture with bromine in chloroform at 40–45° C. affords a mixture of 21-bromo-3α,17α-dihydroxy-16α-methylpregnane-11,20-dione and 21-bromo-3α,17α-dihydroxy-16β-methylpregnane-11,20-dione which upon reaction with potassium acetate and potassium iodide in acetone produces a mixture of 3α,17α,21-trihydroxy-16β-methylpregnane-11,20-dione 21-acetate and 3α,17α,21-trihydroxy-16α-methylpregnane-11,20-dione 21-acetate. To a solution of this mixture in aqueous t-butanol at 10–15° C. is added N-bromosuccinimide to produce a mixture of 17α,21-dihydroxy-16α-methylpregnane-3,11,20-trione 21-acetate and 17α,21-dihydroxy-16β-methylpregnane-3,11,20-trione 21-acetate which on chromatography on neutral alumina and elution with chloroform-benzene (1:1) and benzene yields 17α,21-dihydroxy-16β-methylpregnane-3,11-20-trione 21-acetate (melting point 210–213° C.). Reaction of this compound with bromine in a mixture of acetic acid and chloroform affords the corresponding 4-bromo compound (melting point 165–170° C. dec.) which is converted by reaction with semicarbazide to the 3-semicarbazone of 17α,21-dihydroxy-16β-methyl-4-pregnene-3,11,20-trione 21-acetate. Treatment of this compound with a mixture of acetic acid and pyruvic acid gives 17α,21-dihydroxy-16β-methyl-4-pregnene-3,11,20-trione 21-acetate (melting point 226–232° C.). This latter substance is then hydrolyzed to the C–21 free alcohol by treatment with potassium bicarbonate or potassium hydroxide in aqueous methanol.

EXAMPLE 24

17-20,20-21 bismethylenedioxy-16β-methyl-3-ethylenedioxy-5-pregnen-11-one

17.5 grams of 17-20,20-21 bismethylenedioxy-16β-methyl cortisone (prepared as in Example 23) is dissolved in 890 ml. of benzene, 45 ml. of ethylene glycol and 1.78 grams of p-toluene sulfonic acid, and the mixture heated at reflux for 17.5 hours. During this time a water separator is used to remove the water as it distills. The reaction mixture is then cooled to 20° C., washed with two 200 cc. portions of water, 200 cc. of saturated sodium bicarbonate solution and 200 cc. of water. The organic layer is dried over anhydrous magnesium sulfate and concentrated to a solid. The solid after trituration with ether yields 12.4 grams of 17-20,20-21 bismethylenedioxy-16β-methyl-3-ethylenedioxy-5-pregnen-11-one.

EXAMPLE 25

17-20,20-21 bismethylenedioxy-16β-methyl-1,4-pregnadiene-3,11-dione

To a stirred solution of 1.15 grams (3.08 millimoles) of 16β-methyl-1,4-pregnadien-17α,21-diol-3,11,20-trione in 60 ml. of methylene chloride is added a solution, premixed at 0° C., of 17 ml. of concentrated hydrochloric acid and 17 ml. of a 37% aqueous solution (special:low methanol content) of formaldehyde. The reaction mixture is stirred at room temperature (20–25° C.) for forty hours, after which time 120 ml. of water is added. The layers are separated, and the aqueous layer extracted with three 25 ml. portions of methylene chloride. The combined methylene chloride layer and extracts are washed with 35 ml. of aqueous potassium bicarbonate and three 25 ml. portions of water, dried over anhydrous magnesium sulfate and concentrated to dryness in vacuo. The residue is flushed with benzene, during which process it crystallized. The yield of crystalline 17-20,20-21 bismethylenedioxy - 16β - methyl - 1,4 - pregnadiene-3,11-dione is 1.28 grams.

The 16β - methyl - 1,4 - pregnadien - 17α,21 - diol-3,11,20-trione is prepared by treating 16β-methyl-4-pregnen-17α,21-diol-3,11,20-trione 21-acetate with selenium dioxide in t-amyl alcohol, and then saponifying the 21-acetate ester by warming in methanolic potassium bicarbonate.

EXAMPLE 26

17-20,20-21 bismethylenedioxy-9α-fluoro-4-pregnene-3,11-dione

When 9α-fluoro cortisone is treated according to the procedure set forth in Example 18, using sulfuric acid in place of hydrochloric acid, there is obtained 17-20, 20-21 bismethylenedioxy-9α-fluoro-4-pregnene-3,11-dione, melting point 275-290° C.

EXAMPLE 27

17 - 20,20 - 21 bismethylenedioxy - 3 - pyrrolidyl - 3,5-pregnadien-11-one

500 mg. of 17-20,20-21 bismethylenedioxy-4-pregnene-3,11-dione is dissolved in about 10 ml. of ethanol containing a little methylene chloride. This is concentrated to about 5 ml. to remove methylene chloride. To the concentrate is added 0.5 ml. of pyrrolidine and the mixture heated for one minute on the steam bath. The resultant precipitate is cooled and filtered, and washed with ethanol to give 540 mg. of light yellow prisms, melting point 205–212° C. (dec.), of 17-20,20-21 bismethylene-dioxy-3-pyrrolidyl-3,5-pregnadien-11-one.

Any departure from the above description which conforms to the present invention is intended to be included within the scope of the claims.

What is claimed is:

1. 17-20,20-21 bismethylenedioxy pregnanes having at the 3-position a substituent selected from the class consisting of keto and hydroxy groups and groups convertible thereto by hydrolysis, and having at the 11-position a substituent selected from the class consisting of hydrogen, hydroxy and keto groups; and unsaturated derivatives thereof.

2. 17-20,20-21 bismethylenedioxy pregnanes having at the 3-position a substituent selected from the class consisting of keto and hydroxy groups and groups convertible thereto by hydrolysis, having at the 9-position a substituent selected from the class consisting of halo and hydroxy groups, and having at the 11-position a substituent selected from the class consisting of hydroxy and keto groups; and unsaturated derivatives thereof.

3. 17-20,20-21 bismethylenedioxy pregnanes having at the 3-position a substituent selected from the class consisting of keto and hydroxy groups and groups convertible thereto by hydrolysis, having at the 9-position a substituent selected from the class consisting of hydrogen, halo and hydroxy groups and at the 11-position a substituent selected from the class consisting of hydrogen, hydroxy and keto groups and having at the 16-position a lower alkyl group; and unsaturated derivatives thereof having at least one ring A double bond.

4. 17-20,20-21 bismethylenedioxy pregnanes having an oxygenated function at the 3-position; and nuclearly unsaturated derivatives thereof.

5. 17-20,20-21 bismethylenedioxy - 4 - pregnene - 3,11-dione.

6. 17-20,20-21 bismethylenedioxy - 4 - pregnene-11β-ol-3-one.

7. 17-20,20-21 bismethylenedioxy - 1,4 - pregnadiene-3,11-dione.

8. 17-20,20-21 bismethylenedioxy-1,4-pregnadiene-11β-ol-3-one.

9. 17-20,20-21 bismethylenedioxy-9α-fluoro-4-pregnene-11β-ol-3-one.

10. 17-20,20-21 bismethylenedioxy-9α-fluoro-1,4-pregnadiene-11β-ol-3-one.

11. 17-20,20-21 bismethylenedioxy-16-methyl-4-pregnene-3,11-dione.

12. 17-20,20-21 bismethylenedioxy-16α-methyl-4-pregnene-11β-ol-3-one.

13. 17-20,20-21 bismethylenedioxy-16-methyl-1,4-pregnadiene-11β-ol-3-one.

14. 17-20,20-21 bismethylenedioxy-9α-fluoro-16-methyl-1,4-pregnadiene-11β-ol-3-one.

15. 17-20,20-21 bismethylenedioxy - 16β - methyl-1,4-pregnadiene-3,11-dione.

16. The process for preparing a 17-20,20-21 bismethylenedioxy steroid that comprises reacting a member of the class consisting of 3-oxygenated-17α,21-dihydroxy-20-keto pregnanes and unsaturated derivatives thereof with formaldehyde in the presence of an acid selected from the class consisting of acids having a $-\log k$ of less than 2.25 and formic acid.

17. The process of claim 16 wherein the acid is a mineral acid.

18. The process for preparing a 17-20,20-21 bismethylenedioxy steroid that comprises reacting a member of the class consisting of 3,11-bisoxygenated-17α,21-dihydroxy-20-keto pregnanes and unsaturated derivatives thereof with formaldehyde in the presence of an acid selected from the class consisting of acids having a $-\log k$ of less than 2.25 and formic acid.

19. The process for preparing a 17-20,20-21 bimethylenedioxy steroid that comprises reacting a member of the class consisting of 16-methyl-3,11-bisoxygenated-17α,21-dihydroxy-20-keto pregnanes and unsaturated derivatives thereof with formaldehyde in the presence of an acid selected from the class consisting of acids having a $-\log k$ of less than 2.25 and formic acid.

20. The process which comprises reacting 4-pregnen-17α,21-diol-3,11,20-trione with formaldehyde in the presence of an acid selected from the class consisting of acids having a $-\log k$ of less than 2.25 and formic acid to produce 17-20,20-21 bismethylenedioxy-4-pregnene-3,11-dione.

21. The process which comprises reacting 4-pregnen-17α,21-diol-3,11,20-trione with formaldehyde in the presence of hydrochloric acid in an aqueous:organic solvent two-phase reaction medium to produce 17-20,20-21 bismethylenedioxy-4-pregnene-3,11-dione.

22. The process which comprises reacting 1,4-pregnadien-17α,21-diol-3,11,20-trione with formaldehyde in the presence of an acid selected from the class consisting of acids having a $-\log k$ of less than 2.25 and formic acid to produce 17-20,20-21 bismethylenedioxy-1,4-pregnadiene-3,11-dione.

23. The process which comprises reacting 1,4-pregnadiene-11β,17α,21-triol-3,20-dione with formaldehyde in the presence of an acid selected from the class consisting of acids having a $-\log k$ of less than 2.25 and formic

acid to produce 17-20,20-21 bismethylenedioxy-1,4-pregnadiene-11β-ol-3-one.

24. The process which comprises reacting 9α-fluoro-4-pregnene-11β,17α,21-triol-3,20-dione with formaldehyde in the presence of an acid selected from the class consisting of acids having a —log *k* of less than 2.25 and formic acid to produce 17-20,20-21 bismethylenedioxy-9α-fluoro-4-pregnene-11β-ol-3-one.

25. The process which comprises reacting 16-methyl-4 - pregnen - 17α,21 - diol - 3,11,20 - trione with formaldehyde in the presence of an acid selected from the class consisting of acids having a —log *k* of less than 2.25 and formic acid to produce 17-20,20-21 bismethylenedioxy - 16 - methyl - 4 - pregnene - 3,11 - dione.

26. The process which comprises reacting 16-methyl-4-pregnen - 17α,21 - diol - 3,11,20 - trione with formaldehyde in the presence of hydrochloric acid in an aqueous:organic solvent two-phase reaction medium to produce 17,20,20-21 bismethylenedioxy-16-methyl-4-pregnene-3,11-dione.

27. The process which comprises reacting 16α-methyl-4 - pregnene - 11β,17α,21 - triol - 3,20 - dione with formaldehyde in the presence of an acid selected from the class consisting of acids having a —log *k* of less than 2.25 and formic acid to produce 17-20,20-21 bismethylenedioxy-16α-methyl-4-pregnene-11β-ol-3-one.

28. The process which comprises reacting 16-methyl-

1,4 - pregnadiene - 11β,17α,21 - triol - 3,20 - dione with formaldehyde in the presence of an acid selected from the class consisting of acids having a —log *k* of less than 2.25 and formic acid to produce 17-20,20-21 bismethylenedioxy-16-methyl-1,4-pregnadiene-11β-ol-3-one.

29. The process which comprises reacting 9α-fluoro-16 - methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20-dione with formaldehyde in the presence of an acid selected from the class consisting of acids having a —log *k* of less than 2.25 and formic acid to produce 17-20,20-21 bismethylenedioxy - 9α - fluoro - 16 - methyl - 1,4 - pregnadiene-11β-ol-3-one.

30. The process which comprises reacting 9α-fluoro-16-methyl - 1,4 - pregnadiene - 11β,17α,21 - triol - 3,20-dione with formaldehyde in the presence of hydrochloric acid in an aqueous:organic solvent two-phase reaction medium to produce 17-20,20-21 bismethylenedioxy-9α-fluoro - 16 - methyl - 1,4 - pregnadiene - 11β - ol - 3 - one.

31. The process which comprises reacting 16β-methyl-1,4 - pregnadien - 17α,21 - triol - 3,11,20 - trione with formaldehyde in the presence of an acid selected from the class consisting of acids having a —log *k* of less than 2.25 and formic acid to produce 17-20,20-21 bismethylenedioxy-16β-methyl-1,4-pregnadiene-3,11-dione.

No references cited.