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3,033,873

21-AMINOMETHYL-PREGNENES

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7 Claims. (Cl. 260-397.45)

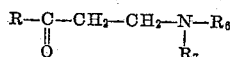
This application is concerned with new and useful steroid compounds. More particularly it is concerned with certain 17 β -(β -dialkyl amino)-propanoyl and 17 β -(β -trialkyl ammonium halide)-propanoyl derivatives of pregnenes which are useful in the preparation of adrenocortically active steroids, the latter being characterized by the presence of a dihydroxylated propanoyl group at the 17 β -position. These latter compounds are described and claimed in copending and concurrently filed patent application, Serial Number 28,180.

The compounds of this invention may be represented by the formula

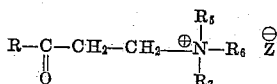


wherein R is a cyclopentanopolyhydrophenanthrene nucleus characterized by having adrenocortical activity when substituted at the 17 β -position with an α -hydroxy acetyl group and M which is located at the 17 β -position replacing the α -hydroxy acetyl group is either a β -dialkyl ammonium propanoyl or a β -trialkyl ammonium halide propanoyl group.

The compounds of this invention may be further defined as compounds having the formula



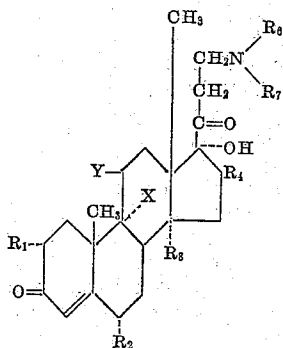
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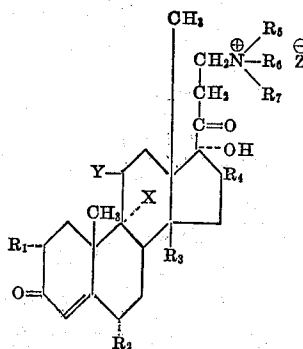
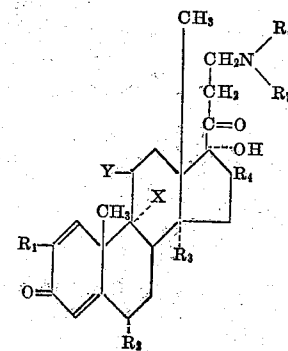
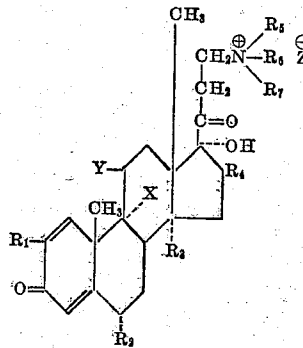
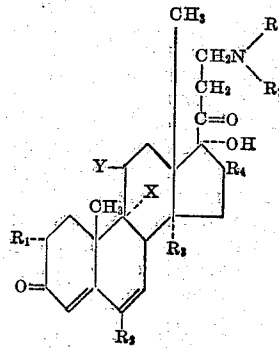
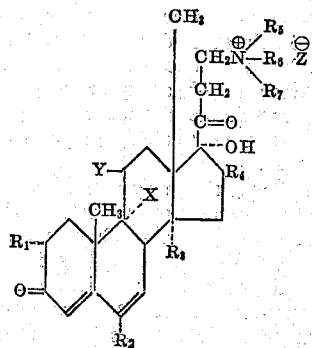
wherein R is an adrenocortically active steroid minus the 17 β -(α -hydroxy acetyl) group and R₅, R₆, and R₇ which may be the same or different in a specific compound are selected from the group consisting of alkyl containing up to four carbon atoms. In the above formula, Z is a halogen atom.

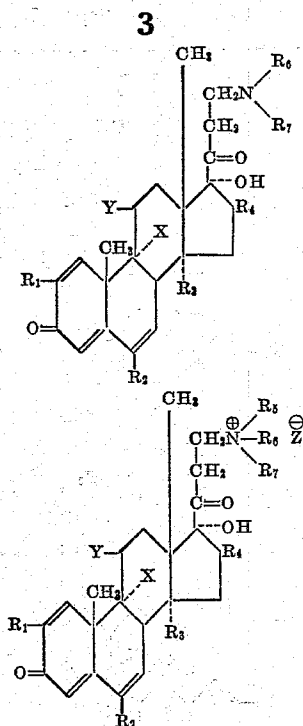
Adrenocortically active steroids now constitute a well-defined class in the art, and include therapeutically active agents having a wide range of applications in the medical field. Cortisone, hydrocortisone, prednisolone, prednisone, 2-methyl prednisolone, 6-methyl prednisolone, 16-methyl prednisolone, 9 α -fluoro hydrocortisone and others have been found to be useful as systemic and topical anti-inflammatory agents. The compounds of this invention are useful in the preparation of compounds of this class.

The preferred compounds within the purview of this invention include those having the formulas:

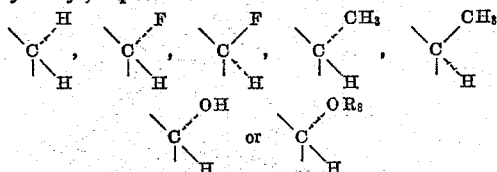


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In the above structures, R₁ is hydrogen or methyl; R₂ is hydrogen, fluorine, chlorine or methyl; R₃ is hydrogen or hydroxyl; R₄ is



wherein R₈ is an acyl group containing only carbon, hydrogen and oxygen, being derived from mono- or dicarboxylic acids containing up to ten carbon atoms; R₅, R₆, R₇ and Z have the same meaning as above; X is hydrogen, halogen, methoxy or ethoxy and Y is keto or β-hydroxyl. The water solubility of compounds derived from dicarboxylic acids is enhanced by conversion to alkali metal or alkaline earth metal salts by reaction with a suitable base such as sodium carbonate or calcium hydroxide. These salts are included within the purview of this invention. In the preferred compounds represented above, the carbon atom at the 16-position is always substituted with at least one hydrogen and at least three of R₁, R₂, R₃ and the second substituent on the number sixteen carbon atom will always be hydrogen.

These compounds are preferred since by reactions set forth more fully below, they are converted into the preferred adrenocortically active dihydroxylated propanoyl steroid compounds described more fully in the aforesaid copending patent application.

Suitable starting materials for the preparation of the new compounds of this invention include those steroid compounds such as hydrocortisone, prednisolone, Δ^6 -hydrocortisone, 9α -fluoro hydrocortisone, 16α -methyl prednisolone, 6α -fluorohydrocortisone and 2-methyl prednisolone, all having an α -hydroxy acetyl group at the 17β -position. Other suitable starting compounds of this nature are well known or can be prepared by procedures known in the art.

Halogen and alkoxy groups are introduced at the 9-position using the procedure of Fried and Sabo described in the Journal of the American Chemical Society, vol. 79, page 1130. This procedure involves dehydration of an 11-hydroxylated compound to give a $\Delta^9(11)$ -compound which is converted to a 9 α ,11 β -bromohydrin by reaction with N-bromoacetamide. This compound is dehydrohalogenated to a 9 β ,11 β -epoxide with potassium acetate.

The epoxide is converted to other halohydrins by reaction with a halogen acid or to an alkoxy compound by reaction with 72% perchloric acid in methyl or ethyl alcohol. The preparation of 9 α -fluoro- $\Delta^{1,4}$ -hydrocortisone and the corresponding $\Delta^{4,6}$ -hydrocortisone by this procedure is set forth in detail by Fried et al. in the Journal of the American Chemical Society, vol. 77, page 4181.

A double bond at the 6(7)-position can be introduced using chloranil in refluxing n-amyl alcohol or preferably tertiary butyl alcohol by the method of Agnello and Laubach as set forth in the Journal of the American Chemical Society, vol. 79, page 1277. This procedure by which a double bond is introduced at the 6(7)-position using a quinone having an oxidation-reduction potential less than -0.5 at a temperature between 70° C. and 190° C. in an inert organic solvent with a boiling point of at least about 70° C. is also described and illustrated in United States Patent No. 2,836,607, issued July 27, 1958.

20 A double bond can be introduced at the 1(2)-position by contacting the steroid compound with selenium dioxide in an inert organic solvent at an elevated temperature. Solvents which are useful for this reaction include, for example, tertiary butanol, tertiary pentanol, benzene, 25 ethylene glycol diethers such as dibutyl Cellosolve, the dipropyl ether of ethylene glycol and various other glycol ethers, phenetole, xylene, dioxane and naphthalene. Preferred conditions include the addition of a lower aliphatic acid, particularly acetic acid to a tert-butanol mixture. In carrying out this reaction, it is generally preferred to utilize temperatures of from about 75° C. to about 200° C. for from about one hour to about one hundred hours. Generally, several molecular proportions of selenium dioxide are added during the reaction period. 35 The application of this reaction is fully illustrated in co-pending patent application, Serial No. 672,550, filed August 18, 1957. It is also described by Meystre et al. in *Helvetica Chimica Acta*, vol. XXXIX, page 734.

Hydrocortisone and cortisone are typical 9-deshalo-
40 Δ^4 -11-oxygenated-21-hydroxy compounds which are use-
ful for the preparation of the valuable intermediates of
this invention. They are well-known therapeutic agents
which have been used for a number of years as anti-
inflammatory agents. Hogg describes the preparation of
45 2-methyl hydrocortisone acetate and 2-methyl cortisone
acetate in the Journal of the American Chemical Society,
vol. 77, page 6401. Spero et al. describe the correspond-
ing 6-methyl compounds and the 6-chloro analogs are
described by Ringold et al. in this same journal at vol. 78,
50 page 6213, and vol. 80, page 6464, respectively. United
States Patent No. 2,838,498, issued June 10, 1958, de-
scribed 6 α -fluoro-hydrocortisone acetate. Shull et al. in
United States Patent No. 2,745,784, issued May 15, 1956,
describes 14 α -hydroxy hydrocortisone and 16 α -hydroxy
55 hydrocortisone is described in the Journal of the American
Chemical Society, vol. 78, page 1909. The compounds
16 β -fluorohydrocortisone and 16 β -fluoroprednisolone are
described in copending patent application, Serial No.
850,032, filed November 11, 1959.

60 Compounds with 16-methyl substituents in both the α and β configuration are known. The compound, 16 α -methyl cortisone acetate is characterized in the Journal of the American Chemical Society, vol. 80, page 3160, and 16 β -methyl cortisone in vol. 80 of this journal at
65 page 4435. The compound, 16 α -fluoro-prednisolone, is described in J.A.C.S., volume 82, page 1250 (March 1960).

Some of the starting compounds set forth above are described as 21-acetates. These, as is well known, can be readily converted to the 21-hydroxy compounds by either alkaline or acid hydrolysis.

Certain of the products referred to above are 11-keto compounds and others are 11 β -hydroxyl compounds. Interconversion of these compounds is readily accomplished by procedures well known in the art. Thus, for

example, an 11 β -hydroxyl group is readily oxidized to an 11-keto group using chromium trioxide in acetic acid or the chromic acid-pyridine complex. An 11-keto group can be reduced to an 11 β -hydroxyl group using lithium aluminum hydride or sodium borohydride. Both of these reagents afford a mixture of 11 α - and 11 β -epimers. The latter reagent is preferred since the product obtained is predominantly of the preferred 11 β -configuration. No matter which reagent is selected, however, there are well-known means for separating the epimers.

The Fried synthesis and/or the selenium dioxide or chloranil reactions of Agnello and Laubach are used to convert these known 9-deshalo- Δ^4 -compounds to the 9-halo- or 9-alkoxy- $\Delta^{1,4}$ -, $\Delta^{4,6}$ - or $\Delta^{1,4,6}$ -21-hydroxy compounds useful as starting materials for the preparation of the compounds of this invention. In fact, many of these compounds are known. For example, 6 α -chloroprednisolone, 6 α -chloro-9 α -fluoroprednisolone acetate and 6 α -chloro-9 α -fluoroprednisone acetate are described in the Journal of the American Chemical Society, vol. 79, page 4818.

As will be recognized by those skilled in the art, it may be necessary to select the order in which certain of the reactions described above are applied to the preparation of the useful starting materials of this invention. Thus, for example, it is best to prepare 9 α -fluorohydrocortisone and to then introduce the 14-hydroxyl group using the procedure of Shull et al. since application of the Fried synthesis to a 14-hydroxylated compound would be complicated by simultaneous dehydration at the 9(11)- and 14,15-positions. Similarly, it is necessary to protect a 16-hydroxyl group, for example, by acylation before oxidation of an 11 β -hydroxyl group.

In the first step for the preparation of the valuable compounds of this invention, the 21-hydroxy compounds are dehydroxylated at the 21-position using p-toluene sulfonic acid and hydrogen iodide. This procedure is well-known and is readily applied by first converting the 21-hydroxyl group to a tosyl ester and then reducing the compound so obtained with hydrogen iodide. The procedure is illustrated in the examples.

The 21-desoxy compound thus prepared is next treated with a mixture of a lower alkyl amine acid addition salt and formaldehyde, the latter conveniently provided as paraformaldehyde. The preferred amine salt is dimethyl amine hydrochloride. It is preferred because it is readily available at a relatively low price and because it gives good yields. However, other symmetrical and non-symmetrical amine salts containing up to four carbon atoms in each alkyl group can be used. These include, for example, diethyl amine sulfate, methyl ethyl amine sulfate, di-n-butyl amine hydrobromide and ethyl isopropyl amine hydriodide. It is preferred to utilize a hydrochloride salt, since these are usually the most readily available and give good yields. Further, it is sometimes desirable to add small amounts of acid before or during the reaction so as to maintain the pH of the reaction mixture at from about 2.5 to about 5. This is most conveniently accomplished with hydrochloric acid.

In carrying out the reaction, the reactants are mixed together in the selected solvent and maintained at a temperature of from about 90° C. to about 140° C. for from about two to about twenty-four hours. The preferred solvents for the reaction are alkanols containing up to five carbon atoms, although other lower aliphatic oxygenated solvents can be used. The preferred alkanols are n-propanol and n-butanol since they reflux at atmospheric pressure within the preferred temperature range. Obviously, however, higher boiling solvents can be used, although usually not at the reflux temperature. Similarly, lower boiling solvents such as methyl and ethyl alcohol are useful if the reaction is carried out under pressure. It is generally most convenient to employ an excess of the paraldehyde and amine salt, to insure as complete a reaction as possible of the more expensive pregnene

derivatives. An excess of from about 50% to about 600% or even more can be used.

The reaction will often be carried out in an inert atmosphere, for example, a nitrogen atmosphere so as to minimize loss of reaction product by side reactions. This, however, is not necessary.

At the end of the reaction period, the desired product may be isolated by evaporating the solvent, preferably in vacuo purified by triturating with hot dilute hydrochloric acid followed, in the case of compounds forming soluble hydrochlorides, with hot water. The water and dilute acid solutions are combined and made basic with dilute aqueous alkali, for example, 10% sodium carbonate, bicarbonate or similar reagent. Occasionally, the pure product will precipitate from the basic solution and may be recovered by filtration. If it does not precipitate, it may be extracted with a water immiscible lower hydrocarbon or halogenated hydrocarbon solvent such as ethylene chloride, chloroform, carbon tetrachloride, chlorobenzene, hexane or octane. The desired product is then recovered from the organic solvent by evaporation in vacuo. The extraction step may also be employed with those products which precipitate from the alkaline solution and thus increase the overall yield.

In the case of compounds forming insoluble hydrochlorides, the residue from the trituration step is recovered by filtration and extracted with an organic solvent such as chloroform which dissolves the impurities. The hydrochloride is recovered by filtration and may be converted to the free base by treatment with dilute aqueous alkali as described above.

The quaternary lower alkyl ammonium halides of this invention are prepared from the foregoing amines by procedures usually employed for this purpose. Thus, for example, the amine is mixed in a lower alkanol solvent, e.g. methanol or ethanol with an alkyl halide containing up to four carbon atoms and simply allowed to stand for from six to about sixteen hours at from about 20° C. to about 30° C. Usually an excess of as much as fifty percent or more of alkyl halide will be used, but this is not essential. The solvent is removed, for example, by evaporation in vacuo and the product recovered as a residue. It may be purified by trituration with ether, acetone or other similar solvent. Methanol and ethanol are the preferred solvents for the reaction because of their good solubility characteristics and also because they can be readily evaporated due to their low boiling point.

The preferred alkyl halides are methyl or ethyl bromide. These are preferred because they are the easiest to obtain and because at the temperature used, they are liquids. Other alkyl halides such as methyl or ethyl chloride can be used but they are usually less convenient since they are gases at ordinary temperature and pressure. Butyl bromide, methyl iodide, or isopropyl chloride may be employed. The iodides are generally not preferred because they form insoluble precipitates when the quaternary compound is decomposed to form the propenoyl compounds in accordance with the equations shown below. They can be used, however, and the product purified by repeated recrystallizations or by standard chromatographic procedures.

The compounds within the scope of this invention are useful because they can be used directly without introducing a microbiological reaction to prepare therapeutically active compounds such as 9 α -fluoro-21-hydroxymethyl- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α ,21-triol-3,20-dione. Compounds of this nature which are described and claimed in copending and concurrently filed patent application, Serial No. 28,180, are useful for the same purposes as hydrocortisone and prednisolone. They are prepared by treatment of the corresponding propenoyl compounds with osmium tetroxide. The propenoyl compounds in turn are prepared from the compounds of this invention by treatment with water or dilute base.

The preparation of 21-hydroxymethyl- $\Delta^{1,4}$ -pregnadiene-

16 α ,17 α ,21-triol-3,11,20-trione 16-hemisuccinate, a typical dihydroxypropanoyl compound, is shown in the series of reactions appearing before the examples.

It should be mentioned that compounds having two hydrogens on the number two carbon atoms should be converted to 3-hydroxy compounds before they are reacted with formaldehyde and the selected amine. Otherwise, it is possible that a dialkylaminomethyl group will substitute at the 2-position as well as the 21-position. Subsequent to the formaldehyde-amine reaction, the ketone group can be regenerated using known oxidative procedures, for example, oxidation with chromic acid, and the double bond reintroduced at the 4-position by bromination followed by dehydrobromination in accordance with known procedures.

One procedure which is especially useful in this respect is that of Mancera et al described in the Journal of the American Chemical Society, 75, 1286 (1953). The crucial step of this procedure is the selective reduction of the 3-keto group of an A-ring saturated steroid of the 5 β -series using sodium borohydride in pyridine. These authors have found that the selective reduction is possible even in the presence of ketone groups at the 11- and the 20-positions. As adapted to the preparation of the compounds of this invention, the A-ring of a Δ^4 -3-keto steroid is saturated by reaction with hydrogen in the presence of a palladium-charcoal catalyst. The 3-ketone group is then reduced using sodium borohydride in pyridine. The resulting 3-hydroxy compound is treated with formaldehyde and an amine as described above.

In an alternative procedure, the 3-keto- Δ^4 -steroid is converted to a 3-hydroxy- Δ^3 -steroid by known procedures. This compound is treated with formaldehyde and an amine and the resulting compound oxidized with chromic acid to regenerate the 3-keto- Δ^4 -structure.

It is specifically intended to include within the purview of this invention new compounds of the class described above in which there is substituted at the 16-position an acylated hydroxyl group containing only carbon, hydrogen, and oxygen derived from mono-carboxylic acids or

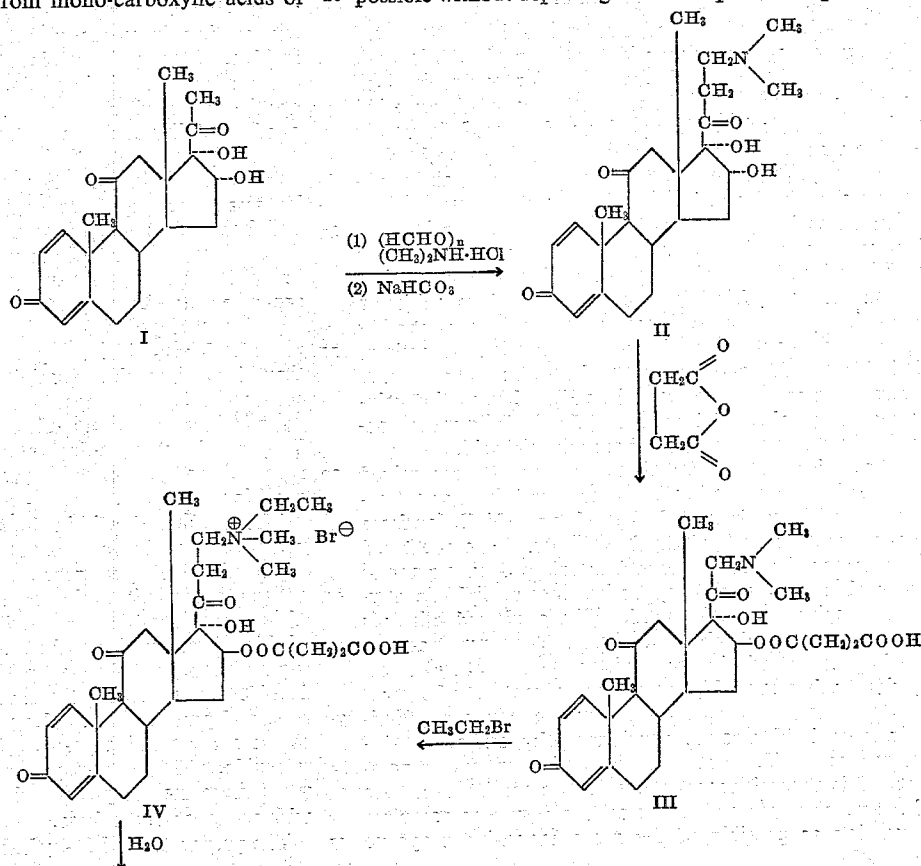
dicarboxylic acids containing up to a total of ten carbon atoms. In the event that the acylated hydroxyl group is derived from a dicarboxylic acid, it is often advantageous to treat the compound with a base derived from alkali metal or alkaline earth metal to prepare a metal salt. These bases include, for example, sodium, potassium, barium and calcium hydroxide as well as the corresponding carbonates and bicarbonates. Products so prepared are especially useful in the preparation of propanoyl compounds because of their increased solubility in water.

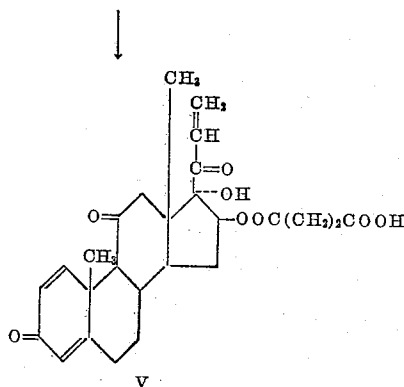
For the preparation of a 16-acylated compound, a 16-hydroxyl compound is esterified by treatment with an acid anhydride for a period of at least six hours. For example, the acetate or hemisuccinate can be prepared by simply allowing the reactants to stand together overnight in a suitable solvent such as pyridine or pyridine in chloroform.

The compounds of this invention are converted to 17 β -propanoyl compounds of which Compound V of the following synthetic outline is illustrative by reaction in an aqueous solution at a pH of from about 7 to about 12 at a temperature of from about 20° C. to about 30° C. for a period of from about 1 to about 6 hours. The process and the compounds prepared by the process are described and claimed in copending and concurrently filed patent application, Serial No. 28,179.

The propanoyl compounds are converted to 17 β -dihydroxylated propanoyl compounds of the class illustrated by Compound VI of the following synthetic outline by reaction with osmium tetroxide in a lower ether solvent containing up to eight carbon atoms at a temperature of from about 20° C. to about 30° C. for a period of from about 16 to about 72 hours and decomposing the resulting osmate ester by bubbling hydrogen sulfide into the reaction mixture.

The following examples are given solely for the purpose of illustration and are not to be construed as limitations of this invention, many variations of which are possible without departing from the spirit or scope thereof.





EXAMPLE I

 $\Delta^{1,4}$ -Pregnadiene-11 β ,17 α -Diol-3,20-Dione

A total of 30 g. of $\Delta^{1,4}$ -pregnadiene-11 β ,17 α ,21-triol-3,20-dione was dissolved in 175 ml. of pyridine in a 500 ml. three-necked flask. The reaction mixture was maintained at approximately -25°C . and 19.1 g. of anhydrous p-toluenesulfonyl chloride in 200 ml. of methylene chloride was added dropwise with stirring. Stirring was continued for 16 hours and the reaction mixture was poured into a separatory funnel. The mixture was washed with 600 ml. of ice cold chloroform containing 100 ml. of water. The aqueous extract was removed and the chloroform layer was washed 4 times with 250 ml. portions of 2 N hydrochloric acid. The organic solution was then washed with 5% aqueous sodium bicarbonate and then with water. It was dried over anhydrous sodium sulfate, filtered and the solvent removed in vacuo to leave $\Delta^{1,4}$ -pregnadiene-11 β ,17 α ,21-triol-3,20-dione 21-tosylate as a residue.

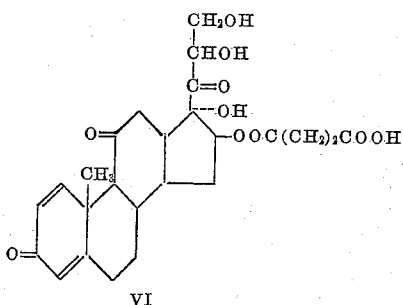
The residue was taken up in 350 ml. of glacial acetic acid containing 26.9 g. of sodium iodide and refluxed with stirring for $\frac{1}{2}$ hour in a nitrogen atmosphere. The solution was cooled and 200 ml. of 0.5 N sodium thiosulfate containing 2 g. of sodium bisulfite was added. The solvent was removed in vacuo using a rotating evaporator, heated by a steam bath and including a Dry-Ice-acetone trap in the train. The residue was diluted with 150 ml. of water. The precipitate was isolated by filtration and washing once with water and again with methanol. The light tan solid which was obtained weighed 15.5 g. and decomposed at 258 to 259°C .

All of the 21-desoxy compounds used in preparing the compounds of this invention are prepared by the foregoing method.

EXAMPLE II

21-Dimethylaminomethyl- $\Delta^{1,4}$ -Pregnadiene-11 β ,17 α -Diol-3,20-Dione

A total of 50 g. of $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione was taken up in 750 ml. of normal propanol containing 24 g. of para-formaldehyde, 80 g. of dimethylamine hydrochloride and 3 ml. of dilute hydrochloric acid. The mixture was refluxed under nitrogen for 16 hours and the hot mixture filtered. The filtrate was evaporated in vacuo and the residue digested in approximately 200 ml. of hot 0.25 N hydrochloric acid. The solid was removed by filtration and the filtrate adjusted to a pH value of approximately 10 with aqueous 10% sodium carbonate. The solution was extracted with chloroform, the chloroform solution dried over anhydrous sodium sulfate, filtered and evaporated in vacuo. The precipitate was triturated with ethyl acetate and recrystallized twice from methyl alcohol. The analytical sample was recrystallized from approximately 10:1 ethyl acetate-ethanol and melted at 187 to 189°C .



Analysis.— $\text{C}_{24}\text{H}_{35}\text{O}_4\text{N}$.—Calcd.: C, 71.78; H, 8.79; N, 3.49. Found: C, 71.68; H, 8.86; N, 4.02.

EXAMPLE III

21-Dimethylaminomethyl- Δ^4 -Pregnene-11 β ,17 α -Diol-3,20-Dione

A total of 25 g. of Δ^5 -pregnene-3 β ,11 β ,17 α -triol-20-one was taken up in 350 ml. of methanol containing 12 g. of para-formaldehyde and 40 g. of dimethylamine hydrochloride. The mixture was maintained at 90°C . under pressure for 24 hours. The hot mixture was filtered and the solution evaporated in vacuo. The residue was digested with hot 0.25 N hydrochloric acid, filtered and the filtrate made basic with 10% sodium carbonate. The solution was extracted with chloroform, the organic layer dried over anhydrous sodium sulfate, filtered and the solvent removed in vacuo to leave the 3 β -hydroxy-21-dimethylaminomethyl compound as a residue. It was converted to the Δ^4 -3-keto by oxidation with chromic acid under standard conditions.

EXAMPLE IV

21-Dimethylaminomethyl-2 α -Methyl- Δ^4 -Pregnene-11 β ,17 α -Diol-3,20-Dione

A total of 35 g. of 2 α -methyl- Δ^4 -pregnene-11 β ,17 α -diol-3,20-dione was taken up in 500 ml. of n-amyl alcohol containing 20 g. of para-formaldehyde, 60 g. of dimethylamine hydrochloride and 2 ml. of dilute hydrochloric acid. The mixture was refluxed for 2 hours in a nitrogen atmosphere and filtered. The residue was digested with 150 ml. of hot 0.25 N hydrochloric acid and filtered. The filtrate was adjusted to an approximate pH of 11 with 10% sodium carbonate. The aqueous solution was extracted with n-hexane. The hexane solution was dried over anhydrous magnesium sulfate, filtered and the desired product obtained by evaporating the solvent in vacuo.

EXAMPLE V

9 α -Fluoro-21-Dimethylaminomethyl- $\Delta^{1,4}$ -Pregnadiene-11 β ,17 α -Diol-3,20-Dione

A total of 10 g. of 9 α -fluoro- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione was taken up in 500 ml. of normal butanol containing 4.8 g. of para-formaldehyde, 16 g. of dimethylamine hydrochloride and 15 drops of 3 N hydrochloric acid. The solution was refluxed under nitrogen for 4 hours during which time an additional 1 ml. of 3 N hydrochloric acid was added to maintain the acidity at a pH of approximately 3. The solvent was removed in vacuo and the residue digested with two 200 ml. portions of hot 0.25 N hydrochloric acid. The residue was washed with water, filtered, the filtrate made basic (pH approximately 10) with 10% aqueous sodium carbonate and extracted with benzene. The benzene solution was dried over anhydrous

11

sodium sulfate, filtered and the solvent removed in vacuo to leave the desired product as a residue.

EXAMPLE VI

21-Methyl-Ethylaminomethyl- $\Delta^{1,4}$ -Pregnadiene-11 β ,17 α -Diol-3,20-Dione

A total of 25 g. of $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione was taken up in 350 ml. of methanol containing 12 g. of para-formaldehyde and 40 g. of methyl ethylamine hydrochloride. The mixture was maintained at 100° C. under pressure for 20 hours. The hot mixture was filtered and the solution evaporated in vacuo. The residue digested with hot 0.25 N hydrochloric acid, filtered and the filtrate made basic with 10% sodium carbonate. The solution was extracted with ethylene dichloride. The organic layer was dried over anhydrous sodium sulfate, filtered and the solvent removed in vacuo to leave the desired product as a residue.

EXAMPLE VII

9 α -Fluoro-21-Dibutylaminomethyl- $\Delta^{1,4}$ -Pregnadiene-11 β ,17 α -Diol-3,20-Dione

A total of 20 g. of 9 α -fluoro- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione was taken up in 750 ml. of normal butanol containing 15 g. of para-formaldehyde, 20 g. of dibutylamine hydrochloride and 15 drops of 3 N hydrochloric acid. The solution was refluxed under nitrogen for 6 hours during which time an additional 1 ml. of 3 N hydrochloric acid was added and maintained the acidity at a pH of approximately 3. The solvent was removed in vacuo and the residue digested with two 300 ml. portions of hot 0.25 N hydrochloric acid. The residue was washed with water, filtered and the filtrate adjusted to a pH of approximately 10 with 10% aqueous sodium carbonate. It was then extracted with chloroform. The chloroform solution was dried over anhydrous sodium sulfate, filtered and the solvent removed in vacuo to leave the desired product as a residue.

EXAMPLE VIII

21-Dimethylaminomethyl-6 α -Methyl- $\Delta^{1,4}$ -Pregnadiene-11 β ,17 α -Diol-3,20-Dione

A total of 35 g. of 6 α -methyl- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione was taken up in 500 ml. of butanol containing 20 g. of para-formaldehyde, 60 g. of dimethylamine hydrobromide and 3 ml. of 40% aqueous hydrobromic acid. The mixture was refluxed for two hours and filtered. The filtrate was evaporated in vacuo and the residue digested with 150 ml. of hot 0.25 N hydrochloric acid and filtered. The filtrate was adjusted to an approximate pH of 10 with 10% sodium carbonate. The aqueous solution was extracted with carbon tetrachloride, the organic solution was dried over anhydrous magnesium sulfate, filtered and the desired product obtained by removing the solvent in vacuo.

The new and useful compounds within the purview of this invention form a large but determinable number. The following dimethylaminomethyl steroid compounds are illustrative of the compounds of this invention which are prepared using the processes set forth in the preceding examples:

$\Delta^{1,4}$ -pregnadiene-11 β ,14 α ,17 α -triol-3,20-dione
6 α -fluoro- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
6 α -fluoro- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
6 α -fluoro-9 α -bromo- $\Delta^{1,4}$ -pregnene-11 β ,17 α -triol-3,20-dione
6 α ,9 α -difluoro- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
6 α -fluoro- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
6 α -fluoro-9 α -bromo- $\Delta^{1,4}$ -pregnadiene-11 β ,14 α ,17 α -triol-3,20-dione
6 α ,9 α -difluoro- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
6 α ,9 α -difluoro- $\Delta^{1,4}$ -pregnadiene-17 α -ol-3,11,20-trione

12

6 α ,9 α -difluoro- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
6 α -fluoro-9 α -chloro- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
6 α -fluoro-9 α -chloro- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
5 6 α -fluoro-9 α -bromo- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
6 α -fluoro-9 α -chloro- $\Delta^{1,4}$ -pregnadiene-17 α -ol-3,11,20-trione
6 α -fluoro-9 α -bromo- $\Delta^{1,4}$ -pregnadiene-17 α -ol-3,11,20-trione
10 6 α -fluoro- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
6 α -fluoro- $\Delta^{1,4}$ -pregnadiene-17 α -ol-3,11,20-trione
6 α -fluoro- $\Delta^{1,4}$ -pregnene-11 β ,16 α -diol-3,20-dione
6 α -fluoro- $\Delta^{1,4}$ -pregnene-11 β ,16 α ,17 α -triol-3,20-dione
6 α -fluoro- $\Delta^{1,4}$ -pregnene-16 α ,17 α -diol-3,11,20-trione
15 6 α -fluoro- $\Delta^{1,4}$ -pregnadiene-11 β ,16 α ,17 α -triol-3,20-dione
6 α -fluoro- $\Delta^{1,4}$ -pregnadiene-16 α ,17 α -diol-3,11,20-trione
16 α -methyl- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
16 β -methyl- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
16 α -methyl-9 α -bromo- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
20 16 β -methyl-9 α -bromo- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
16 α -methyl-9 α -fluoro- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
25 16 β -methyl-9 α -fluoro- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
16 α -methyl-9 α -fluoro- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
16 β -methyl-9 α -fluoro- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
30 6 α -methyl- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
6 α -methyl- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
6 α -methyl- $\Delta^{1,4}$ -pregnadiene-17 α -ol-3,11,20-trione
9 α -fluoro- $\Delta^{4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
35 9 α -fluoro- $\Delta^{4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
9 α -fluoro- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
9 α -chloro- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
9 α -bromo- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
9 α -iodo- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
40 9 α -methoxy- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
9 α -ethoxy- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
9 α -fluoro- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
9 α -chloro- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
9 α -bromo- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
45 9 α -iodo- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
9 α -methoxy- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
9 α -ethoxy- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
9 α -fluoro- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
6 α -methyl-9 α -fluoro- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
50 6 α -methyl-9 α -bromo- $\Delta^{1,4}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
6 α -methyl-9 α -fluoro- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
6 α -methyl-9 α -bromo- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
55 2 α -methyl- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
2 α -methyl-9 α -bromo- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
2 α -methyl-9 α -fluoro- $\Delta^{1,4}$ -pregnene-11 β ,17 α -diol-3,20-dione
2 α -methyl-9 α -fluoro- $\Delta^{1,4}$ -pregnene-17 α -ol-3,11,20-trione
60 $\Delta^{1,4,6}$ -pregnatriene-11 β ,17 α -diol-3,20-dione
 $\Delta^{4,6}$ -pregnadiene-11 β ,14 α ,17 α -triol-3,20-dione
 $\Delta^{4,6}$ -pregnadiene-14 α ,17 α -diol-3,11,20-trione
 $\Delta^{4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 $\Delta^{1,4,6}$ -pregnatriene-11 β ,14 α -triol-3,20-dione
65 16 α -methyl- $\Delta^{4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
16 β -methyl- $\Delta^{4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
16 α -methyl-9 α -bromo- $\Delta^{4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
16 β -methyl-9 α -bromo- $\Delta^{4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
70 16 α -methyl-9 α -fluoro- $\Delta^{4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
16 β -methyl-9 α -fluoro- $\Delta^{4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
75 16 β -methyl-9 α -fluoro- $\Delta^{4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione

13

16 α -methyl-9 α -fluoro- $\Delta^{1,4,6}$ -pregnatriene-11 β ,17 α -diol-3,20-dione
 6-methyl- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 6-methyl- $\Delta^{1,4,6}$ -pregnatriene-11 β ,17 α -diol-3,20-dione
 6-methyl- $\Delta^{1,4,6}$ -pregnadiene-17 α -ol-3,11,20-trione
 6-methyl- $\Delta^{1,4,6}$ -pregnatriene-17 α -ol-3,11,20-trione
 9 α -fluoro- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 9 α -chloro- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 9 α -bromo- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 9 α -iodo- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 9 α -methoxy- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 9 α -ethoxy- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 9 α -fluoro- $\Delta^{1,4,6}$ -pregnadiene-17 α -ol-3,11,20-trione
 9 α -chloro- $\Delta^{1,4,6}$ -pregnadiene-17 α -ol-3,11,20-trione
 9 α -bromo- $\Delta^{1,4,6}$ -pregnadiene-17 α -ol-3,11,20-trione
 9 α -iodo- $\Delta^{1,4,6}$ -pregnadiene-17 α -ol-3,11,20-trione
 9 α -methoxy- $\Delta^{1,4,6}$ -pregnadiene-17 α -ol-3,11,20-trione
 9 α -ethoxy- $\Delta^{1,4,6}$ -pregnadiene-17 α -ol-3,11,20-trione
 9 α -fluoro- $\Delta^{1,4,6}$ -pregnatriene-11 β ,17 α -diol-3,20-dione
 6-methyl-9 α -fluoro- $\Delta^{1,4,6}$ -pregnatriene-11 β ,17 α -diol-3,20-dione
 6-methyl-9 α -bromo- $\Delta^{1,4,6}$ -pregnatriene-11 β ,17 α -diol-3,20-dione
 6-methyl-9 α -fluoro- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 6-methyl-9 α -bromo- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 2 α -methyl- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 2 α -methyl- $\Delta^{1,4,6}$ -pregnadiene-17 α -ol-3,11,20-trione
 2 α -methyl-9 α -bromo- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 2 α -methyl-9 α -fluoro- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 2 α -methyl-9 α -fluoro- $\Delta^{1,4,6}$ -pregnadiene-17 α -ol-3,11,20-trione
 6 α -chloro- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 16 α -fluoro- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 9 α ,16 α -difluoro- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione
 16 β -fluoro- $\Delta^{1,4,6}$ -pregnatriene-11 β ,17 α -diol-3,20-dione
 9 α ,16 β -difluoro- $\Delta^{1,4,6}$ -pregnadiene-11 β ,17 α -diol-3,20-dione

Although only dimethylaminomethyl compounds are shown above, it should be understood that other amines are identically prepared by replacing the dimethylamine acid addition salt with other amine acid addition salts such as dibutylamine hydriodide, methylethylamine hydrobromide, di-isopropylamine sulfate or ethyl-n-propyl amine hydrochloride.

EXAMPLE IX

The above compounds are converted to 16 α -esters using standard procedures. The esters prepared include formates, acetates, propionates, butyrates, malonates, maleates, fumarates, hemisuccinates, hemiglutarates and decanoates. Those esters derived from dicarboxylic acids are converted to alkali metal and alkaline earth metal salts by reaction with a molar proportion of a base such as sodium or potassium bicarbonate in accordance with procedures well known in the art.

EXAMPLE X

21-Dimethylaminomethyl- $\Delta^{1,4}$ -Pregnadiene-11 β ,17 α -Diol-3,20-Dione Methobromide

A solution of 7.5 g. of the compound prepared in Example II in 180 ml. of methanol and 80 ml. of methyl bromide is allowed to stand overnight and then evaporated to dryness in vacuo. The residue is triturated with acetone and the desired product recovered by filtration. An additional crop of the quaternary can be obtained by evaporation of the acetone filtrate and this is purified by trituration with methanol and recovered by filtration.

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EXAMPLE XI

21-Dimethylaminomethyl- Δ^4 -Pregnene-11 β ,17 α -Diol-3,20-Dione Butyl-Chloride

A solution of 7.5 g. of the product obtained in Example III in 150 ml. of ethanol containing a 50% molar excess of butyl chloride is allowed to stand at 25° C. for 16 hours and then evaporated to dryness in vacuo. The residue is triturated with acetone and the desired product recovered by filtration.

EXAMPLE XII

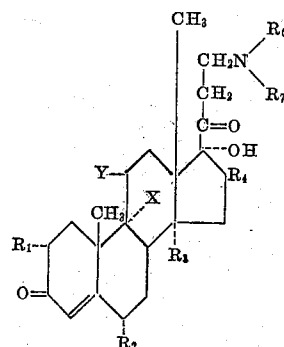
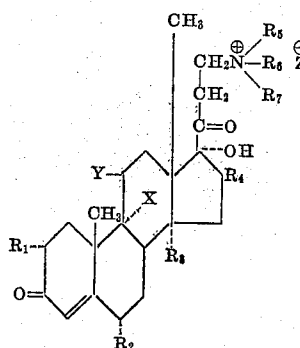
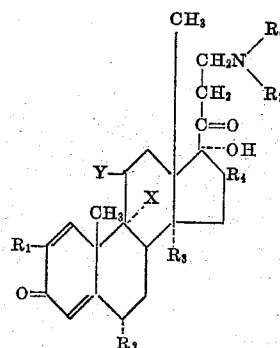
21-Dimethylaminomethyl-2 α -Methyl- Δ^4 -Pregnene-11 β ,17 α -Diol-3,20-Dione Diethiodide

A solution of 8 g. of the product obtained in Example IV in 200 ml. of methanol containing a 20% molar excess of ethyl iodide is allowed to stand for 20 hours at approximately 28° C. and then evaporated to dryness in vacuo. The residue is triturated with ether and the desired product recovered by filtration.

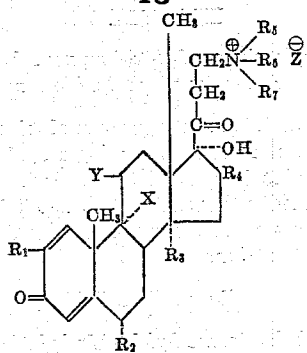
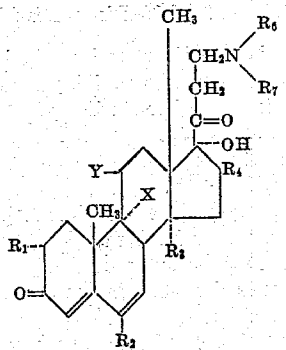
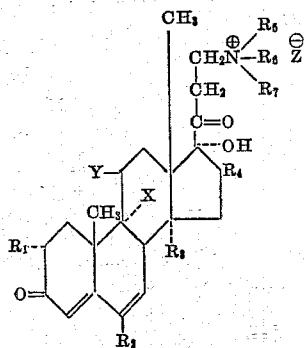
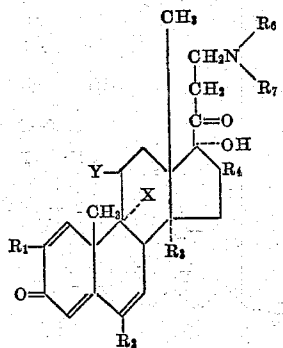
Other quaternary alkyl ammonium halide salts of this invention are prepared from the amines prepared in accordance with the procedures of the foregoing examples using the methods described in the last three examples.

What is claimed is:

1. A compound selected from the group consisting of those having the formulae:



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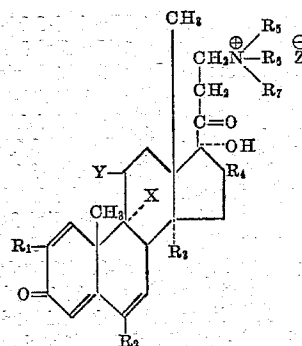
and

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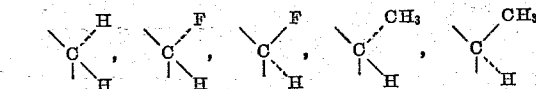
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wherein R_1 is selected from the group consisting of hydrogen and methyl; R_2 is selected from the group consisting of hydrogen, fluorine, chlorine and methyl; R_3 is selected from the group consisting of hydrogen and hydroxyl; R_4 is selected from the group consisting of

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and

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R_5 is selected from the group consisting of hydrogen and acyl groups containing only carbon, hydrogen and oxygen and derived from mono- and dicarboxylic acids containing up to ten carbon atoms; R_5 , R_6 and R_7 are alkyl containing up to four carbons; X is selected from the group consisting of hydrogen, halogen, methoxy and ethoxy; Y is selected from the group consisting of keto and β -hydroxyl; and Z is halogen.

2. 21 - dimethylaminomethyl - $\Delta^{1,4}$ - pregnadiene - 11 β , 17 α -diol-3,20-dione.

3. 21 - dimethylaminomethyl - Δ^4 - pregnene - 11 β , 17 α -diol-3,20-dione.

4. 9 α - fluoro - 21 - dimethylaminomethyl - $\Delta^{1,4}$ - pregnadiene-11 β , 17 α -diol-3,20-dione.

5. 21 - methylethylaminomethyl - $\Delta^{1,4}$ - pregnadiene-11 β , 17 α -diol-3,20-dione.

6. 21 - dimethylaminomethyl - 6 α - methyl - $\Delta^{1,4}$ - pregnadiene-11 β , 17 α -diol-3,20-dione.

7. 21 - dimethylaminomethyl - $\Delta^{1,4}$ - pregnadiene - 11 β , 17 α -diol-3,20-dione methobromide.

References Cited in the file of this patent

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