United States Patent Office

3,033,855
Patented May 8, 1962

1

3,033,855

21-AMINOMETHYL DERIVATIVES OF PROGESTERONE

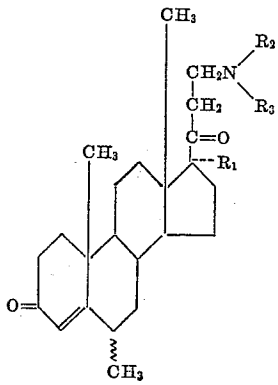
Rudolph G. Berg, Groton, Sanford K. Figdor, Gales Ferry, and Gerald D. Laubach, Niantic, Conn., assignors to Chas. Pfizer & Co., Inc., New York, N.Y., a corporation of Delaware

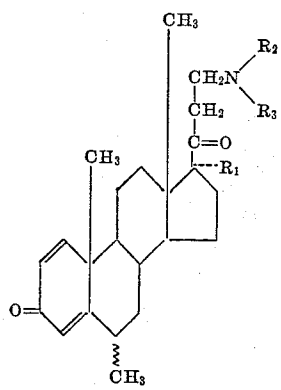
No Drawing. Filed May 11, 1960, Ser. No. 28,181
2 Claims. (Cl. 260—239.5)

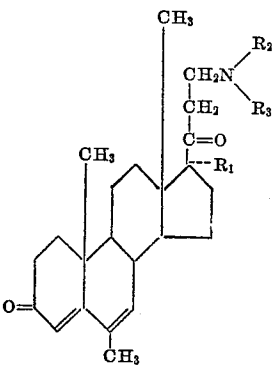
This application is concerned with new and useful steroid compounds and with therapeutically useful compositions containing them. More particularly, it is concerned with certain 21-aminomethyl derivatives of progesterone characterized by having progestational activity. It is concerned also with pharmaceutically acceptable acid addition and quaternary ammonium derivatives of these compounds which also have progestational activity.

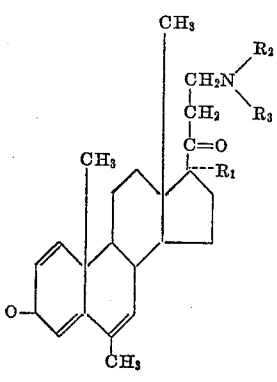
Apart from their therapeutic utility, the compounds of this invention are also useful for the preparation of certain 21-methylene derivatives of progesterone and 21-halomethyl derivatives of progesterone both of which have useful progestational activity. These classes of compounds are described and claimed in copending and concurrently filed patent applications, Serial Nos. 28,182 and 28,183.

Compounds within the purview of this invention are selected from the group consisting of those represented by the formulas:

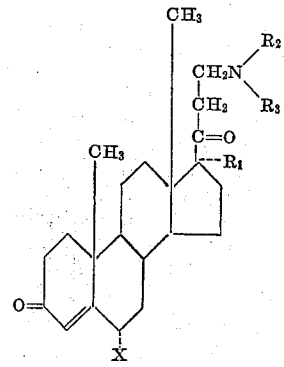


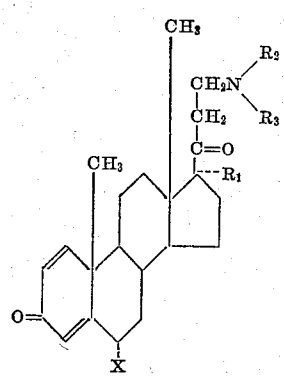


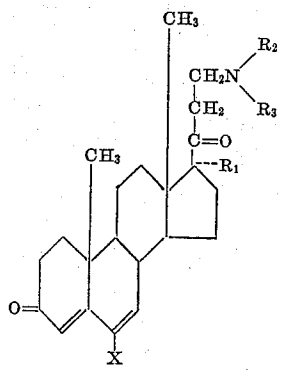


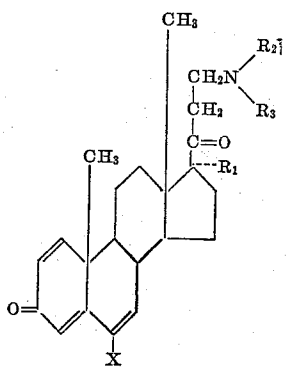


2









wherein X is selected from the group consisting of hydrogen, fluorine, chlorine and bromine; R_1 is selected from the group consisting of hydrogen, hydroxyl and acylated hydroxyl, an acyl group being derived from monocarboxylic acids containing only carbon, hydrogen and oxygen up to a total of ten carbon atoms and R_2 and R_3 which may be the same or different in a particular compound, are selected from the group consisting of hydrogen and alkyl groups containing up to four carbon atoms and further groups wherein R_2 and R_3 are joined and together with the nitrogen atom to which they are attached form a heterocyclic ring selected from the group consisting of pyrrolidine, piperidine and morpholine; and pharmaceutically acceptable acid addition and quaternary alkyl ammonium derivatives thereof, an alkyl group containing up to four carbon atoms, R_2 and R_3 always being other than hydrogen in the said quaternary alkyl ammonium derivatives.

The $\Delta^{1,4}$- and $\Delta^{1,4,6}$-compounds within the scope of this valuable new series of progestational agents in which R_2 and R_3 are both alkyl groups or joined to form heterocyclic rings are prepared directly by reaction of the corresponding progesterone derivative with an amine addition salt and formaldehyde. Amine salts which can be used include mineral acid addition salts of symmetrical and non-symmetrical dialkylamines in which each alkyl group contains up to four carbon atoms, pyrrolidine, piperidine and morpholine. They include, for example, diethylamine sulfate, methyl ethyl amine sulfate, di-n-butyl amine hydrobromide, ethyl isopropylamine hydriodide, pyrrolidine hydrochloride, piperidine nitrate or morpholine phosphate. It is preferred to utilize a hydrochloride salt, since these are usually most readily available and

give good yields. Further, it is sometimes desirable to add small amounts of acid before or during the reaction to maintain the reaction mixture at a pH of from about 2.5 to 5.0. This is most conveniently accomplished with hydrochloric acid.

With compounds having no double bond at the 1,2-position or even with those having a double bond at the 1,2-position in which one or both of R_2 and R_3 are hydrogens, it is necessary to react a 3-hydroxy compound with an amine salt and formaldehyde, preferably, dimethyl amine hydrochloride and formaldehyde to form a 3-hydroxy-21-dimethylaminomethyl compound. A molecule of dimethyl amine is then eliminated for example, by forming a quaternary ammonium compound which is then treated with water or an aqueous alkali for from about 1 to about 6 hours at a temperature of from about 20° C. to about 30° C. to form a 21-methylene compound, the 3-hydroxyl group is oxidized to a keto group and the resulting compound is treated with ammonia or an amine as the free base to form the desired 3-keto-Δ^4-21-substituted compound. The 21-methylene compounds formed in this type of reaction and certain other 21-methylene progestational agents are described and claimed in copending and concurrently filed patent application, Serial No. 28,182.

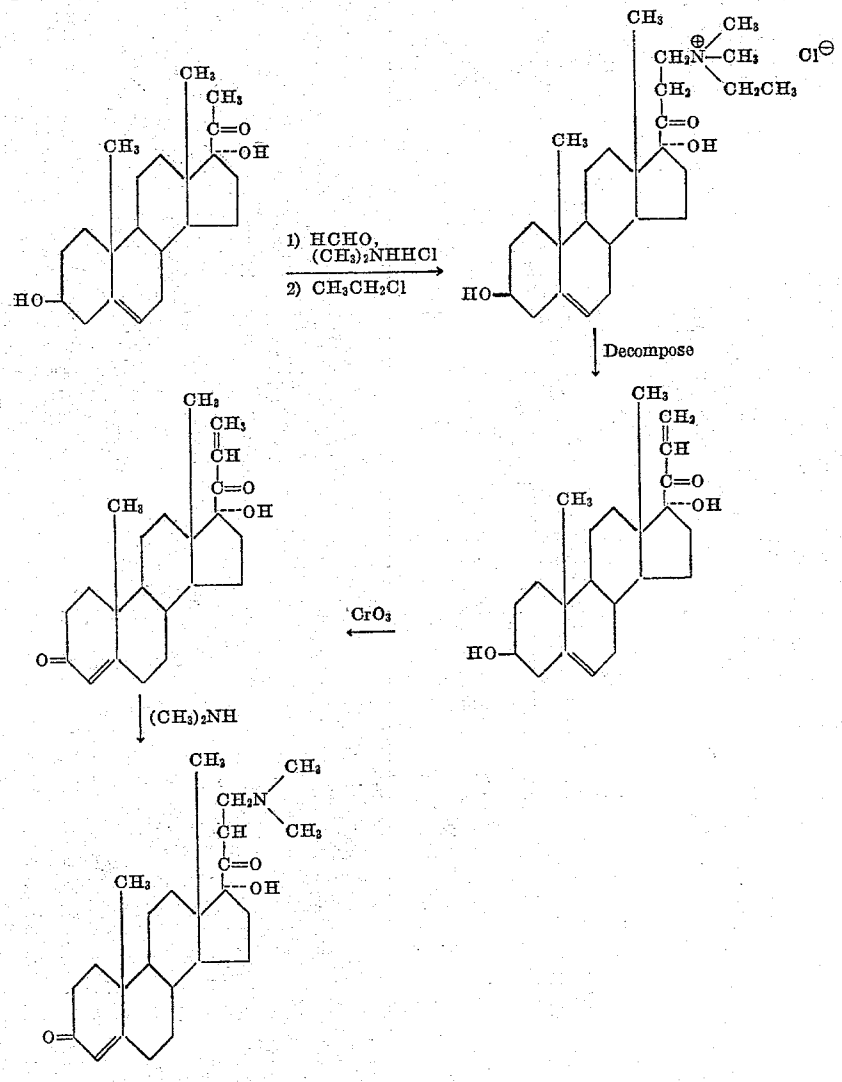
This sequence of reactions is shown below. It is necessary to employ this sequence because the reaction of a 3-keto-1,2-dihydro steroid with an amine salt and formaldehyde results in substitution at the 2-position as well as the 21-position, and because the reaction with formaldehyde and an amine is not operable with ammonia or primary amines.

If the 3-keto-Δ^4-compound is to be substituted at the 6-position, this sequence will be slightly modified as explained hereinafter.

For the preparation of the other amines of this invention, 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 alcohols are useful if the reaction is carried out under pressure. It is generally most convenient to employ an excess of the paraldehyde i.e. formaldehyde and amine salt, to insure as complete a reaction as possible of the more expensive pregnene derivatives. A molar excess of from about 50% to about 600% or even more can be used. The amount is not critical.

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 acid addition salts 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.

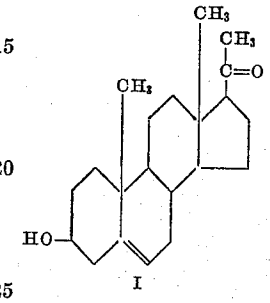
In the case of compounds forming insoluble acid addition salts, the residue from the trituration step is recovered by filtration and extracted with an organic solvent such as chloroform which dissolves the impurities. The salt is recovered by filtration and may be converted to the free base by treatment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

The amine prepared as described above may be converted to a quaternary ammonium halide using procedures generally 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 about 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 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.

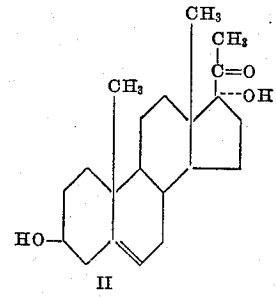
The preferred alkyl halides are methyl or ethyl bromide. These are preferred because they are the easiest to obtain and because at the temperatures used, they are liquids. Other alklyl halides such as methyl or ethyl chloride can be used but they are usually less convenient since they are gases at ordinary temperature and pressure. Butyl bromide, methyl iodide, or isopropyl chloride may be employed.

As stated above, it is intended to include within the purview of the instant invention various pharmaceutically acceptable acid addition salts, that is, acid addition salts which the free bases of the compounds of this invention form with acids having a pharmaceutically acceptable anion. The term "pharmaceutically acceptable anion" has a definite meaning to one skilled in the art. It is defined as a non-toxic anion of any of the simple acids commercially used therapeutically to neutralize basic medicinal agents when the salts thereof is to be administered to a human host. These acids include, for example, hydrochloric, hydrobromic, hydriodic, sulfuric, succinic, maleic, tartaric, citric, glycolic and others. The pharmaceutical activity of the molecule is primarily a function of the cation, the anion serving chiefly to supply electrical neutrality. These various pharmaceutically acceptable acid addition salts are prepared by procedures well known in the art. For example, one may simply treat the steroid with an aqueous solution of the selected pharmaceutically acceptable acid. Alternatively, one may employ various anion exchange resins in accordance with well-known methods.

The basic starting materials used in the preparation of the valuable compounds of this invention include pregnenolone (I) and 17-hydroxypregnenolone (II).



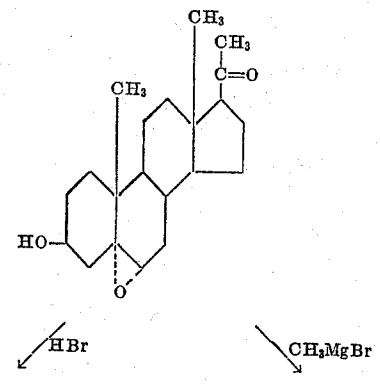
I

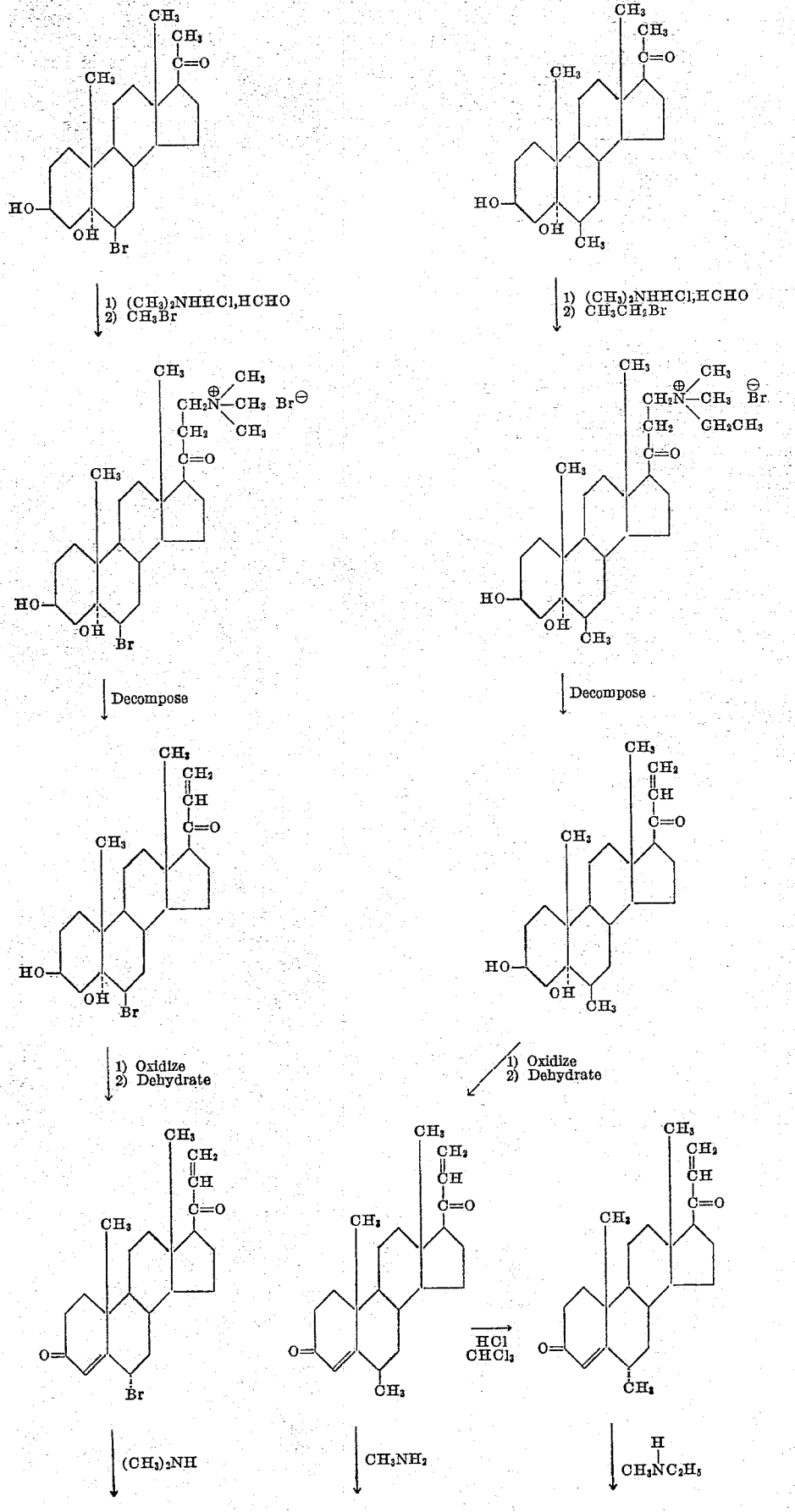


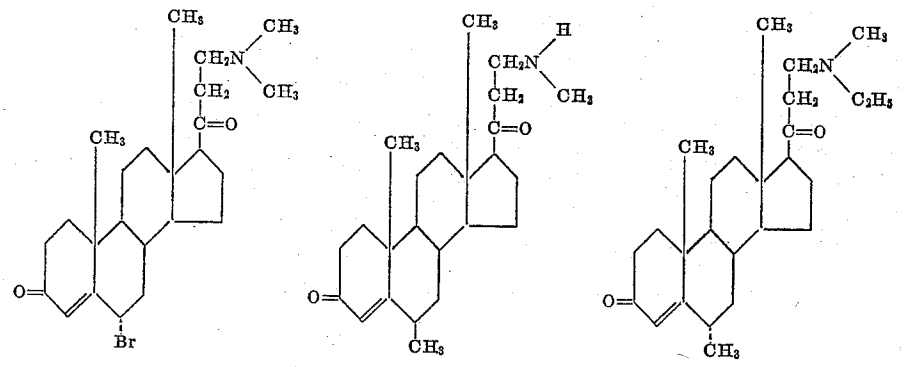
II

These compounds may be used directly as described above for the preparation of 1,2,6,7-tetrahydro-Δ^4-compounds within the purview of this invention. They also serve as starting materials for the 6-substituted-1,2,6,7-tetrahydro-Δ^4-compounds within the purview of the invention. For the preparation of 6-methyl, 6-chloro or 6-bromo compounds, the starting compound is first converted to a 5α,6α-epoxide by reaction with peracetic or perbenzoic acid. The epoxide ring is next opened with methyl magnesium bromide, hydrogen chloride or hydrogen bromide. These reactions produce respectively 5α-hydroxy-6β-methyl, 5α-hydroxy-6β-chloro and 5α-hydroxy-6β-bromo steroids. The compounds thus produced are converted to 21-methylene compounds by the route described above, oxidized with chromic acid and dehydrated with 0.005N sodium hydroxide in aqueous methanol to produce 3-keto-Δ^4-methylene compounds and finally reacted with ammonia or an amine to produce the desired 3-keto-$\Delta^{4,6}$-substituted 21-amino compounds. In the case of the chloro and bromo compounds, the halogen atom epimerizes during the dehydration step. With 6-methyl steroids, a mixture of 6α and 6β-methyl compounds is obtained with the latter predominating. The mixture is separated by crystallization, for example, from isopropanol or acetone-water. The 6β-epimer may be epimerized by treatment with anhydrous acid in a halogenated solvent, for example, anhydrous hydrogen chloride in chloroform.

Some aspects of the foregoing series of reactions are illustrated in the following sequence. The 5α,6α-epoxide compound is known in both the pregnenolone and the 16-hydroxypregnenolone series.

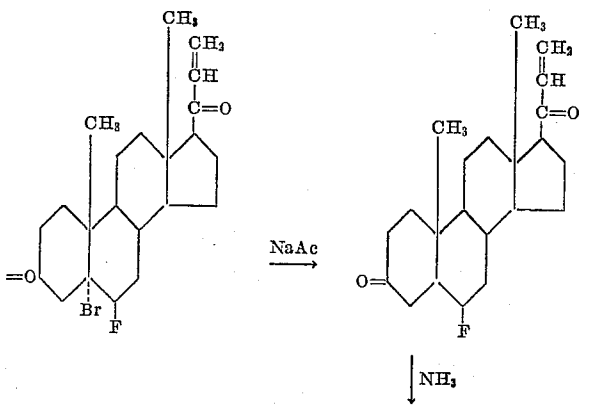


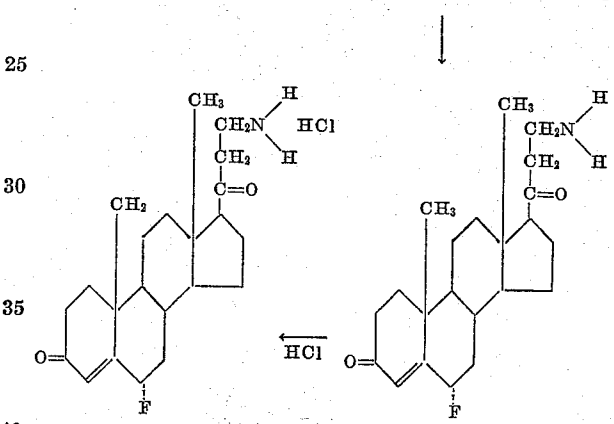

1) $(CH_3)_2NHHCl,HCHO$
2) CH_3Br
1) $(CH_3)_2NHHCl,HCHO$
2) CH_3CH_2Br
Decompose
Decompose
1) Oxidize
2) Dehydrate
1) Oxidize
2) Dehydrate
HCl
$CHCl_3$
$(CH_3)_2NH$
CH_3NH_2
$CH_3NC_2H_5$



A similar series of reactions would be employed with 17-hydroxypregnenolone.

A somewhat different sequence is used to produce 6α-fluoro substituted compounds. In this sequence, pregnenolone or the 17-hydroxylated compound is reacted with from about 1.05 to about 1.15 molar equivalents of N-bromoacetamide and from about 25 to about 100 molar equivalents of anhydrous hydrogen fluoride at from about −80° C. to about −50° C. for a period of from about 1 to about 16 hours in a solvent system containing 20% tetrahydrofuran and 80% methylene dichloride by volume. The reaction produces a 5α-bromo-6β-fluoro compound which is converted to a 21-methylene compound by the series of reactions shown above. The compound is then oxidized to a 3-keto steroid with chromic acid and the bromine atom is removed by reaction with from about a molar equivalent to about a 200% molar excess of an alkaline reagent such as sodium or potassium acetate in an alkanol, ester or ketone solvent containing up to nine carbon atoms at a temperature of from about 50° C. to about 130° C. for a period of from about one half to about six hours. The resulting 3-keto-Δ^4-6β-fluoro-21-methylene compound is then reacted with an amine to produce a 21-aminomethyl compound. The fluorine atom is epimerized to the 6α-configuration by reaction with an acidic reagent such as anhydrous hydrogen chloride or anhydrous hydrogen bromide in a halogenated hydrocarbon solvent containing up to two carbon atoms or an ester or alkanol solvent containing up to three carbon atoms at a temperature of from about −5° C. to about 10° C. for a period of from about 2 to about 4 hours. The reaction sequence starting with 6α-bromo-6α-fluoro-21-methylene-pregnane-3,20-dione is shown below.





The sequence shown is also applicable to 17-hydroxypregnenolone.

It should be mentioned that one may select to introduce the double bonds in the 1,2- or 4,6-positions of the 6α-chloro-, 6α-bromo-, 6α-methyl-, 6β-methyl- or 6-fluoro-21-methylene compounds described above and to use the thus produced $\Delta^{1,4}$-, $\Delta^{4,6}$- or $\Delta^{1,4,6}$-steroids as substrates for the production of the 21-amino compounds of this invention. Alternatively, one can utilize the procedures described below.

Progesterone, 17-acetoxyprogesterone and the corresponding 6α-fluoro, 6α-bromo-, 6α-chloro, 6α-methyl and 6β-methyl compounds are all known. They serve as excellent starting materials for the preparation of $\Delta^{1,4}$- and $\Delta^{1,4,6}$-compounds within the scope of this invention since double bonds at these positions can be readily introduced using known reactions.

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, 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. The application of this reaction is fully illustrated in copending 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.

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.

The application of these reactions to the preparation of 6α-chloro-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione 17-acetate (1-dehydro-6α-chloro-17-acetoxyprogesterone) and the correspoding 6-dehydro compound is shown in Vol. 81 of the Journal of the American Chemical Society at page 3485. This article also shows the application of the reactions to various other progesterone derivatives which serve as starting materials for the preparation of the valuable compounds of this invention.

This is not the reaction of choice with Δ^6-6-bromo compounds. These compounds, i.e., 6-bromo-$\Delta^{4,6}$-steroids, are best prepared by another procedure set forth hereinafter.

Many progesterone derivatives having a double bond in the 1-position are known and these can be used directly with an amine salt and formaldehyde to prepare compounds of this invention. Chloranil and other ketones can be advantageously employed to prepare Δ^6-compounds, except in the case of 6-bromo compounds.

With 6-bromo compounds, the Δ^6-steroid is best prepared by dibrominating a $\Delta^{4,6}$-substrate with a slight molar excess of bromine in a halogenated hydrocarbon or lower aliphatic acid solvent such as chloroform, methylene chloride or ethylene chloride, acetic acid or propionic acid or mixtures of these at a temperature of from about 20° C. to about 40° C. for a period of from about 3 to about 5 hours. The 6β,7α-dibromo compound thus prepared in dehydrobrominated in a nitrogenous base, e.g. pyridine or collidine in accordance with the usual procedure, i.e., heating at about 40° C. to about 175° C. for from about 1 to about 5 hours. Dioxane and other lower aliphatic ethers are also useful solvents.

Compounds within the purview of this invention having a 17α-acylated hydroxyl group are prepared by conventional methods, i.e., treatment with the corresponding anhydride and a catalytic amount of p-toluenesulfonic acid. In the event the anhydride is a solid, a reaction inert solvent such as a halogenated hydrocarbon solvent containing up to two carbon atoms is employed. With liquid anhydrides such ac acetic anhydride or caproic anhydride, the anhydride itself serves as a solvent. Reaction is effected by simply maintaining the reactants in admixture with each other at a temperature of from about 20° C. to about 30° C. for a period of from about 10 to about 24 hours.

It will be recognized that this treatment results in an acid salt of the acylated compound. It may be isolated by evaporation of the solvent. Purification may be effected by washing the residue with dilute aqueous alkali, for example, 2% sodium carbonate solution. This treatment also results in neutralization of the acid and formation of the free base. Alternatively, the free base may be obtained by evaporating the solvent, dissolving the residue in a minimum amount of water and adding sufficient aykaline reagent to neutralize the solution. Most of the free base will precipitate and may be recovered by filtration. Any free base remaining in the solution may be isolated by extraction with an organic solvent followed by the usual treatment.

With compounds in which one or both of R_2 and R_3 are hydrogen, acylation should be effected before reaction with the amine.

The biologically active compounds of this invention may be administered alone or in combination with other active ingredients. They will usually be administered in compositions together with pharmaceutically acceptable carriers, the choice of which is determined by the preferred route of administration, the solubility of the compound and the standard pharmaceutical practice. In general, the dosage of these compounds is of the same order of magnitude as the dosage of 17-acetoxyprogesterone, 17-ethynyl - 19 - nortestosterone and 17α-ethynyl-$\Delta^{5(10)}$-estren-17α-ol-3-one, and they are used to treat the same types of physiological conditions. Because of their high order of progestational activity, it is sometimes possible to utilize these compounds at a lower dosage level than is usually employed with the above-mentioned progestational agents.

As stated above, the compounds of this invention are also useful for the preparation of certain 21-methylene derivatives of progesterone and 21-halomethyl derivatives of progesterone both of which have useful progestational activity. The reactions by which these compounds are prepared are described more fully in the above-identified copending patent applications. In general, the 21-methylene compounds are prepared by mixing quaternary ammonium halides of this invention 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 21-halomethyl compounds are prepared by reaction between the steroid substrate and anhydrous hydrogen halide in a reaction inert organic solvent at a temperature of from about 10° C. to about 30° C. for a period of from about 10 minutes to about 80 minutes. The reaction with hydrogen fluoride is catalyzed with antimony trifluoride, and the reaction with hydrogen chloride is catalyzed with stannic chloride. They may also be prepared in situ by formation of the quaternary in an alkanol such as methanol or ethanol and decomposition of the quaternary by refluxing for about from 5 to about 24 hours. The reaction is best carried out on an acid addition salt in the presence of an alkaline reagent such as sodium acetate. An excess of alkyl halide and base is used. The amount is not critical, for example, 50% to 1000% molar excess may be used.

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.

In the following examples, compounds marked with an asterisk are used for the preparation of compounds within the scope of this invention, but are not themselves embodied within the class.

EXAMPLE I*

21-Dimethylaminomethyl-Δ^5-Pregnene-3β-Ol-20-One

A total of 50 grams of Δ^5-pregnene-3β-ol-20-one was taken up in 750 ml. of propanol containing 24 grams of paraldehyde, 80 grams 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 0.25N 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 organic layer dried over anhydrous sodium sulfate, filtered and the solvent removed in vacuo to leave the desired product as a residue.

EXAMPLE II*

21-Dimethylaminomethyl-Δ^5-Pregnene-3β-Ol-20-One Methyl Bromide

A solution of 7.5 grams of the product prepared in Ex-

ample I in 180 ml. of methanol and 80 ml. of methyl bromide was allowed to stand overnight and then evaporated to dryness in vacuo. The residue was triturated with acetone and the desired product recovered by filtration. An additional crop of the quaternary compound was obtained by evaporation of the acetone filtrate and purified by trituration with methanol.

EXAMPLE III*

21-Methylene-Δ^5-Pregnene-3β-Ol-20-One

A solution of 200 mg. of the product prepared in the previous example in 10 ml. of water was prepared and clarified by filtration. To the solution, there was added 68 mg. of sodium bicarbonate in 2 ml. of water at 25° C. A white precipitate of the desired product separated immediately. The suspension was stirred for 1 hour, filtered, washed with water and dried in vacuo.

EXAMPLE IV*

21-Methylene-Δ^4-Pregnene-3,20-Dione

To a solution of 5 grams of the product prepared in the previous example, there was added 15 ml. of a solution of chromium trioxide in 9:1-acetic acid-water solution containing 76 mg. of chromium trioxide per ml. of solution. The mixture was kept at room temperature during the addition and for an additional 4 hours. At the end of this period, 2 ml. of concentrated hydrochloric acid was added and the solution was maintained at room temperature for an additional 5 hours. The desired compound was precipitated by the addition of water and recovered by filtration.

EXAMPLE V*

21-Methylene-$\Delta^{1,4}$-Pregnadiene-3,20-Dione

A mixture of 0.8 gram of the product prepared in the previous example, 0.8 gram of freshly sublimed selenium dioxide and 10 ml. of tert-butanol was heated in a nitrogen atmosphere for 10½ hours at 175° C. The solution was filtered and the desired product precipitated by the addition of water. It was isolated by filtration.

EXAMPLE VI*

21-Methylene-$\Delta^{4,6}$-Pregnadiene-3,20-Dione

A mixture containing 1.3 grams of the product prepared in Example IV and 3.5 grams of chloranil in 30 ml. of tert-butanol was refluxed in a nitrogen atmosphere for 18 hours. The reaction mixture was then diluted with 250 ml. of chloroform. The solvent solution was washed with several small portions of 5% sodium hydroxide solution and then with water. It was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to leave the desired product as a residue.

EXAMPLE VII*

21-Methylene-$\Delta^{1,4,6}$-Pregnatriene-3,20-Dione

A mixture containing 2.6 grams of the product prepared in Example V and 6.0 grams of chloranil in 60 ml. of tert-butanol was refluxed in a nitrogen atmosphere for 18 hours. The reaction mixture was then diluted with 250 ml. of chloroform. The solvent solution was washed with several small portions of 5% sodium hydroxide solution and then with water. It was dried over anhydrous sodium sulfate, filtered and concentrated in vacuo to leave the desired product as a residue.

EXAMPLE VIII

21-Methylaminomethyl-Δ^4-Pregnene-3,20-Dione

A total of 10 grams of 21 methylene-Δ^4-pregnene-3,20-dione was taken up in 200 ml. of a 1:1 water-dioxane mixture and a 30% molar excess of methylamine was bubbled into the solution. The solution was maintained at 20° C. for 6 hours and the desired product obtained by removal of the solvent in vacuo.

The following compounds were similarly prepared:

21-methylaminomethyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-methylaminomethyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-methylaminomethyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

EXAMPLE IX

21-Aminomethyl-Δ^4-Pregnene-3,20-Dione

A total of 10 grams of 21-methylene-Δ^4-pregnene-3,20-dione was taken up in 300 ml. of tetrahydrofuran and an equimolar portion of aqueous ammonium hydroxide was added. The solution was maintained at 20° C. for 1 hour and the desired product obtained by evaporation of the solvent.

The following compounds were similarly prepared:

21-aminomethyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-aminomethyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-aminomethyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

EXAMPLE X

21-Butylaminomethyl-Δ^4-Pregnene-3,20-Dione

A total of 10 grams of 21-methylene-Δ^4-pregnene-3,20-dione was taken up in 300 ml. of a 1:1 water-dioxane mixture. A 30% molar excess of butylamine was added and the mixture was maintained at 40° C. for 6 hours. The solvent was removed in vacuo to leave the desired product as a residue.

The following compounds were similarly prepared:

21-butylaminomethyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-butylaminomethyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-butylaminomethyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-dipropylaminomethyl-Δ^4-pregnene-3,20-dione
21-dipropylaminomethyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-dipropylaminomethyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-dipropylaminomethyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-pyrrolidinoaminomethyl-Δ^4-pregnene-3,20-dione
21-pyrrolidinoaminomethyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-pyrrolidinoaminomethyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-pyrrolidinoaminomethyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-piperidinoaminomethyl-Δ^4-pregnene-3,20-dione
21-piperidinoaminomethyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-piperidinoaminomethyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-piperidinoaminomethyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-morpholinoaminomethyl-Δ^4-pregnene-3,20-dione
21-morpholinoaminomethyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-morpholinoaminomethyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-morpholinoaminomethyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

EXAMPLE XI*

6β-Bromo-Pregnane-3β,5α-Diol-20-One

A solution of 7 grams of 5α,6α-oxido-pregnane-3β-ol-20-one in 700 ml. of dry 1:1 benzene-ether was prepared. A 50% molar excess of anhydrous hydrogen bromide was bubbled through the solution at 25° C. over a period of 4 hours. The solution was washed with 5% aqueous sodium carbonate until neutral and then with an equal volume of water. It was dried over anhydrous magnesium sulfate, filtered and concentrated to dryness.

This same procedure was employed to prepare 6β-chloro-pregnane-3β,5α-diol-20-one.

EXAMPLE XII*

21-Dimethylaminomethyl-6β-Bromo-Pregnane-3β,5α-Diol-20-One

A total of 25 grams of the product prepared in the previous example was taken up in 350 ml. of methanol containing 12 grams of paraldehyde and 40 grams of dimethylamine sulfate. The mixture was maintained at 100° C. under pressure for 20 hours. The hot mixture was then 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 ethylene chloride. The organic layer was dried over anhy-

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

This same procedure was used to prepare 21-dimethylaminomethyl-6β-chloro-pregnane-3β,5α-diol-20-one.

The procedure of Example II was used to convert these compounds to the following quaternary ammonium compounds:

21-dimethylaminomethyl-6β-bromo-pregnane-3β,5α-diol-20-one methyl bromide
21-dimethylaminomethyl-6β-chloro-pregnane-3β,5α-diol-20-one methyl bromide

EXAMPLE XIII*

21-Methylene-6β-Bromo-Pregnane-3β,5α-Diol-20-One

A solution containing 2 grams of the quaternary ammonium compound prepared in the previous example was dissolved in 500 ml. of water and stirred at 20° C. for 6 hours. The desired product separated and was recovered by filtration.

This same procedure was employed for the preparation of 21-methylene-6β-chloro-pregnane-3β,5α-diol-20-one.

EXAMPLE XIV*

21-Methylene-6β-Bromo-Pregnane-5α-Ol-3,20-Dione

Chromic anhydride (0.125 gram) was added to 15 ml. of pyridine at approximately 5° C. The mixture was allowed to warm spontaneously to room temperature. To this solution, there was added 2.5 grams of the product prepared in the previous example in 20 ml. of pyridine and the mixture was allowed to stand at room temperature for 24 hours. It was extracted with ether and the ether solution washed twice with 5% aqueous hydrochloric acid and then with water. The ether layer was dried over anhydrous sodium sulfate, filtered and the desired product obtained by removal of the ether in vacuo.

EXAMPLE XV*

21-Methylene-6α-Bromo-Δ^4-Pregnene-3,20-Dione

A total of 5 grams of the product prepared in the previous example was taken up in 200 ml. of 0.005 N sodium hydroxide in aqueous tert-butanol and the mixture maintained at 25 to 30° C. for 17 hours. The mixture was neutralized by the cautious addition of 2% hydrochloric acid and extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate, filtered and the desired product obtained by removal of the solvent in vacuo.

This same procedure was employed to prepare 21-methylene-6α-chloro-Δ^4-pregnene-3,20-dione.

EXAMPLE XVI*

21-Methylene-6α-Bromo-$\Delta^{1,4}$-Pregnadiene-3,20-Dione

This compound and 21-methylene-6α-chloro-$\Delta^{1,4}$-pregnadiene-3,20-dione were each prepared from the products of the previous example using the procedure of Example V.

EXAMPLE XVII*

21-Methylene-6-Chloro-$\Delta^{4,6}$-Pregnadiene-3,20-Dione

This compound was prepared from the 6-chloro product of Example XVI using the procedure of Example VI.

EXAMPLE XVIII*

21-Methylene-6-Chloro-$\Delta^{1,4,6}$-Pregnatriene-3,20-Dione

This compound was prepared from the product of Example XVII using the procedure of Example VI.

EXAMPLE XIX

21-Methylaminomethyl-6α-Bromo-Δ^4-Pregnene-3,20-Dione

A total of 10 grams of 21-methylene-6α-bromo-Δ^4-pregnene-3,20-dione was taken up in 600 ml. of 1:1 water-dioxane containing an equimolar portion of methylamine. The mixture was maintained at 20° C. for 6 hours and the desired product recovered by evaporation of the solvent in vacuo.

This identical procedure was used to prepare the following compounds:

21-methylaminomethyl-6α-chloro-Δ^4-pregnene-3,20-dione
21-methylaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-methylaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-methylaminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-methylaminoethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

EXAMPLE XX

21-Aminomethyl-6α-Bromo-Δ^4-Pregnene-3,20-Dione

This compound and 21-aminomethyl-6α-chloro-Δ^4-pregnene-3,20-dione were prepared from the products of Example XV using the procedure of Example IX.

The following compounds were similarly prepared:

21-aminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-aminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-aminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-aminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

EXAMPLE XXI

21-Butylaminomethyl-6α-Bromo-Δ^4-Pregnene-3,20-Dione

This compound and 2-butylaminomethyl-6α-chloro-Δ^4-pregnene-3,20-dione were prepared from the products of Example VX using the procedure of Example X.

The following compounds were similarly prepared:

21-butylaminomethyl-6α-chloro-Δ^4-pregnene-3,20-dione
21-butylaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-butylaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-butylaminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-butylaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-dipropylaminomethyl-6α-bromo-Δ^4-pregnene-3,20-dione
21-dipropylaminomethyl-6α-chloro-Δ^4-pregnene-3,20-dione
21-dipropylaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-dipropylaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-dipropylaminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-dipropylaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-pyrrolidinoaminomethyl-6α-bromo-Δ^4-pregnene-3,20-dione
21-pyrrolidinoaminomethyl-6α-chloro-Δ^4-pregnene-3,20-dione
21-pyrrolidinoaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-pyrrolidinoaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-pyrrolidinoaminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-pyrrolidinoaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-piperidinoaminomethyl-6α-bromo-Δ^4-pregnene-3,20-dione
21-piperidinoaminomethyl-6α-chloro-Δ^4-pregnene-3,20-dione
21-piperidinoaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-piperidinoaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-3,20-dione

21-piperidinoaminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-piperidinoaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-morpholinoaminomethyl-6α-bromo-Δ^{4}-pregnene-3,20-dione
21-morpholinoaminomethyl-6α-chloro-Δ^{4}-pregnene-3,20-dione
21-morpholinoaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-morpholinoaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-morpholinoaminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-morpholinoaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

EXAMPLE XXII*

21-Dimethylaminomethyl-6β-Methyl-Pregnane-3β,5α-Diol-20-One

This compound was prepared from the known compound, 6β-methyl-pregnane-3β,5α-diol-20-one using the procedure of Example I.

EXAMPLE XXIII*

21-Dimethylaminomethyl-6β-Methyl-Pregnane-3β,5α-Diol-20-One Methyl Bromide

This compound was prepared from the product of the previous example using the procedure of Example II.

EXAMPLE XXIV*

21-Methylene-6β-Methyl-Pregnane-3β,5α-Diol-20-One

This compound was prepared from the product of the previous example using the procedure of Example III.

EXAMPLE XXV*

21-Methylene-6β-Methyl-Pregnane-5α-Ol-3,20-Dione

This compound was prepared from the product of the previous example using the procedure of Example IV.

EXAMPLE XXVI*

21-Methylene-6α-Methyl-Δ^{4}-Pregnene-3,20-Dione and 21-Methylene-6β-Methyl-Δ^{4}-Pregnene-3,20-Dione

These compounds were prepared from the product of the previous example by dehydration in 0.005N sodium hydroxide according to the procedure of Example XV. A mixture of isomers was obtained and separated by crystallization from acetone and water. The 6β-methyl compound predominated and precipitated from solution first.

EXAMPLE XXVII*

21-Methylene-6α-Methyl-$\Delta^{1,4}$-Pregnadiene-3,20-Dione and 21-Methylene-6β-Methyl-$\Delta^{1,4}$-Pregnadiene-3,20-Dione

These compounds were prepared from the product of Example XXVI using the procedure of Example V.

EXAMPLE XXVIII*

21-Methylene-6-Methyl-$\Delta^{4,6}$-Pregnadiene-3,20-Dione

This compound was prepared from the products of Example XXVI using the procedure of Example VI.

EXAMPLE XXIX*

21-Methylene-6-Methyl-$\Delta^{1,4,6}$-Pregnatriene-3,20-Dione

This compound was prepared from the product of the previous example using the procedure of Example VII.

EXAMPLE XXX

21-Methylaminomethyl-6α-Methyl-Δ^{4}-Pregnene-3,20-Dione

This compound and 21-methylaminomethyl-6β-methyl-Δ^{4}-pregnene-3,20-dione were prepared from the product of Example XXVI using the procedure of Example VIII.

The following compounds were similarly prepared:

21-methylaminomethyl-6α-methyl-$\Delta^{1,4}$-pregnadine-3,20-dione
21-methylaminomethyl-6β-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-methylaminomethyl-6-methyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-methylaminomethyl-6-methyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

EXAMPLE XXXI

21-Aminomethyl-6α-Methyl-Δ^{4}-Pregnene-3,20-Dione

This compound and 21-aminomethyl-6β-methyl-Δ^{4}-pregnene-3,20-dione were prepared from the products of Example XXVI using the procedure of Example IX.

The following compounds were similarly prepared:

21-aminomethyl-6α-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-aminomethyl-6β-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-aminomethyl-6-methyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-aminomethyl-6-methyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

EXAMPLE XXXII

21-Butylaminomethyl-6α-methyl-Δ^{4}-Pregnene-3,20-Dione

This compound and 21-butylaminomethyl-6β-methyl-Δ^{4}-pregnene-3,20-dione were prepared from the products of Example XXVI using the procedure of Example X.

The following compounds were similarly prepared:

21-butylaminomethyl-6α-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-butylaminomethyl-6β-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-butylaminomethyl-6-methyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-butylaminomethyl-6-methyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-dipropylaminomethyl-6α-methyl-Δ^{4}-pregnene-3,20-dione
21-dipropylaminomethyl-6β-methyl-Δ^{4}-pregnene-3,20-dione
21-dipropylaminomethyl-6α-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-dipropylaminomethyl-6β-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-dipropylaminomethyl-6-methyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-dipropylaminomethyl-6-methyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-pyrrolidinoaminomethyl-6α-methyl-Δ^{4}-pregnene-3,20-dione
21-pyrrolidinoaminomethyl-6β-methyl-Δ^{4}-pregnene-3,20-dione
21-pyrrolidinoaminomethyl-6α-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-pyrrolidinoaminomethyl-6β-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-pyrrolidinoaminomethyl-6-methyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-pyrrolidinoaminomethyl-6-methyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-piperidinoaminomethyl-6α-methyl-Δ^{4}-pregnene-3,20-dione
21-piperidinoaminomethyl-6β-methyl-Δ^{4}-pregnene-3,20-dione
21-piperidinoaminomethyl-6α-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-piperidinoaminomethyl-6β-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-piperidinoaminomethyl-6-methyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-piperidinoaminomethyl-6-methyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-morpholinoaminomethyl-6α-methyl-Δ^{4}-pregnene-3,20-dione

21-morpholinoaminomethyl-6β-methyl-Δ^4-pregnene-3,20-dione
21-morpholinoaminomethyl-6α-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-morpholinoaminomethyl-6β-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-morpholinoaminomethyl-6-methyl-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-morpholinoaminomethyl-6-methyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

EXAMPLE XXXIII*

5α-Bromo-6β-Fluoro-Pregnane-3β-Ol-20-One

Anhydrous hydrogen fluoride (168 grams) was collected directly from the cylinder in a polyethylene vessel and cooled to −70° C. It was cautiously added to dry tetrahydrofuran also cooled to −70° C. and contained in a polyethylene vessel. Considerable heat was evolved, the temperature rising to approximately 0° C. The mixture was recooled to −70° C. and then added with vigorous stirring to a suspension of finely powdered N-bromoacetamide (26.8 grams) and Δ^5-pregnene-3β-ol-20-one (55 grams) in 430 ml. of methylene chloride at −70° C. After maintaining for 1 hour at between −50° C. and −70° C., the entire reaction mixture was poured cautiously into 3 liters of water containing 800 grams of potassium carbonate, the mixture being stirred during the addition. The organic layer was separated and the aqueous layer extracted with two 100 ml. portions of methylene chloride. The combined organic layers were washed with 5% potassium bicarbonate solution until neutral, then with water and finally dried over anhydrous sodium sulfate. The solvent was removed in vacuo to leave the desired product as a residue.

EXAMPLE XXXIV*

21-Dimethylaminomethyl-5α-Bromo-6β-Fluoro-Pregnane-3β-Ol-20-One

This compound was prepared from the product of the previous example using the procedure of Example I.

EXAMPLE XXXV*

Dimethylaminomethyl-5α-Bromo-6β-Fluoro-Pregnane-3β-Ol-20-One Methyl Bromide

This compound was prepared from the product of the previous example using the procedure of Example II.

EXAMPLE XXXVI*

21-Methylene-5α-Bromo-6β-Fluoro-Pregnane-3β-Ol-20-One

This compound was prepared from the product of the previous example using the procedure of Example III.

EXAMPLE XXXVII*

21-Methylene-5α-Bromo-6β-Fluoro-Pregnane-3,20-One

This compound was prepared from the product of the previous example using the procedure of Example XIV.

EXAMPLE XXXVIII*

21-Methylene-6β-Fluoro-Δ^4-Pregnene-3,20-Dione

A mixture containing 5 grams of the product of the previous example and an equimolar portion of anhydrous sodium acetate was refluxed in 300 ml. of methanol for 40 minutes. The mixture was poured into 2 liters of water and the desired product which precipitated was collected by filtration.

EXAMPLE XXXIX*

21-Methylene-6β-Fluoro-$\Delta^{1,4}$-Pregnadiene-3,20-Dione

This compound was prepared from the product of the previous example using the procedure of Example V.

EXAMPLE XL*

21-Methylene-6-Fluoro-$\Delta^{4,6}$-Pregnadiene-3,20-Dione

This compound was prepared from the product of Example XXXVIII using the procedure of Example VI.

EXAMPLE XLI*

21-Methylene-6-Fluoro-$\Delta^{1,4,6}$-Pregnatriene-3,20-Dione

This compound was prepared from the product of the previous example using the procedure of Example V.

EXAMPLE XLII

21-Methylaminomethyl-6α-Fluoro-Δ^4-Pregnene-3,20-Dione

This compound was prepared from the product of Example XXXVIII. The 6β-fluoro compound was first prepared according to the procedure of Example XIX. Isomerization was effected by bubbling anhydrous HCl into a chloroform solution while maintaining the temperature at −50° C. The hydrochloride which formed was neutralized with aqueous bicarbonate solution and the desired product isolated by evaporating the solvent after drying over sodium sulfate.

The following compounds were similarly prepared:

21-methylaminomethyl-6α-fluoro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-methylaminomethyl-6-fluoro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-methylaminomethyl-6-fluoro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

EXAMPLE XLIII

21-Aminomethyl-6α-Fluoro-Δ^4-Pregnene-3,20-Dione

This compound was prepared from the product of Example XXXVIII. The 6β-compound was first prepared using the procedure of Example XX. Isomerization was effected using the procedure of Example XLII.

The following compounds were similarly prepared:

21-aminomethyl-6α-fluoro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-aminomethyl-6-fluoro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-aminomethyl-6-fluoro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

EXAMPLE XLIV

21-Butylaminomethyl-6α-Fluoro-Δ^4-Pregnene-3,20-Dione

This compound was prepared from the product of Example XXXVIII. The 6β-compound was first prepared using the procedure of Example XXI. Isomerization was effected as in Example XLII.

The following compounds were similarly prepared:

21-butylaminomethyl-6α-fluoro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-butylaminomethyl-6-fluoro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-butylaminomethyl-6-fluoro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-dipropylaminomethyl-6α-fluoro-Δ^4-pregnene-3,20-dione
21-dipropylaminomethyl-6α-fluoro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-dipropylaminomethyl-6-fluoro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-dipropylaminomethyl-6-fluoro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-pyrrolidinoaminomethyl-6α-fluoro-Δ^4-pregnene-3,20-dione
21-pyrrolidinoaminomethyl-6α-fluoro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-pyrrolidinoaminomethyl-6-fluoro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-pyrrolidinoaminomethyl-6-fluoro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-piperidinoaminomethyl-6α-fluoro-Δ^4-pregnene-3,20-dione

21-piperidinoaminomethyl-6α-fluoro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-piperidinoaminomethyl-6-fluoro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-piperidinoaminomethyl-6-fluoro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-morpholinoaminomethyl-6α-fluoro-Δ^{4}-pregnene-3,20-dione
21-morpholinoaminomethyl-6α-fluoro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-morpholinoaminomethyl-6-fluoro-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-morpholinoaminomethyl-6-fluoro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

The procedures illustrated in the above examples were repeated using Δ^{5}-pregnene-3β,17α-ol-20-one (17-hydroxy pregnenolone) as the starting material to prepare the following compounds:

21-methylaminomethyl-Δ^{4}-pregnene-17α-ol-3,20-dione
21-methylaminomethyl-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-methylaminomethyl-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-methylaminomethyl-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-butylaminomethyl-Δ^{4}-pregnene-17α-ol-3,20-dione
21-butylaminomethyl-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-butylaminomethyl-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-butylaminomethyl-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-dipropylaminomethyl-Δ^{4}-pregnene-17α-ol-3,20-dione
21-dipropylaminomethyl-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-dipropylaminomethyl-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-dipropylaminomethyl-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-Δ^{4}-pregnene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-piperidinoaminomethyl-Δ^{4}-pregnene-17α-ol-3,20-dione
21-piperidinoaminomethyl-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-piperidinoaminomethyl-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-piperidinoaminomethyl-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-morpholinoaminomethyl-Δ^{4}-pregnene-17α-ol-3,20-dione
21-morpholinoaminomethyl-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-morpholinoaminomethyl-$\Delta^{4,6}$-pregnadiene-17α-ol,3,20-dione
21-morpholinoaminomethyl-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-methylaminomethyl-6α-bromo-Δ^{4}-pregnene-17α-ol-3,20-dione
21-methylaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-methylaminomethyl-6α-chloro-Δ^{4}-pregnene-17α-ol-3,20-dione
21-methylaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-methylaminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-methylaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-aminomethyl-6α-bromo-Δ^{4}-pregnene-17α-ol-3,20-dione
21-aminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-aminomethyl-6α-chloro-Δ^{4}-pregnene-17α-ol-3,20-dione
21-aminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-aminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-aminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-butylaminomethyl-6α-bromo-Δ^{4}-pregnene-17α-ol-3,20-dione
21-butylaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-butylaminomethyl-6α-chloro-Δ^{4}-pregnene-17α-ol-3,20-dione
21-butylaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-butylaminomethyl-6α-chloro-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-butylaminomethyl-6α-chloro-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-dipropylaminomethyl-6α-bromo-Δ^{4}-pregnene-17α-ol-3,20-dione
21-dipropylaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-dipropylaminomethyl-6α-chloro-Δ^{4}-pregnene-17α-ol-3,20-dione
21-dipropylaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-dipropylaminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-dipropylaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6α-bromo-Δ^{4}-pregnene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6α-chloro-Δ^{4}-pregnene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6α-bromo-Δ^{4}-pregnene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6α-chloro-Δ^{4}-pregnene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6α-bromo-Δ^{4}-pregnene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6α-chloro-Δ^{4}-pregnene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6-chloro-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-methylaminomethyl-6α-methyl-Δ^{4}-pregnene-17α-ol-3,20-dione
21-methylaminomethyl-6β-methyl-Δ^{4}-pregnene-17α-ol-3,20-dione
21-methylaminomethyl-6α-methyl-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione

21-methylaminomethyl-6β-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-methylaminomethyl-6-methyl-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-methylaminomethyl-6-methyl-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-aminomethyl-6α-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-aminomethyl-6β-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-aminomethyl-6α-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-aminomethyl-6β-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-aminomethyl-6-methyl-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-aminomethyl-6-methyl-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-butylaminomethyl-6α-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-butylaminomethyl-6β-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-butylaminomethyl-6β-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-butylaminomethyl-6α-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-butylaminomethyl-6β-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-butylaminomethyl-6-methyl-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-butylaminomethyl-6-methyl-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-dipropylaminomethyl-6α-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-dipropylaminomethyl-6β-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-dipropylaminomethyl-6α-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-dipropylaminomethyl-6β-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-dipropylaminomethyl-6-methyl-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-dipropylaminomethyl-6-methyl-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6α-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6β-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6α-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6β-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6-methyl-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6-methyl-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6α-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6β-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6α-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6β-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6-methyl-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6-methyl-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6α-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6β-methyl-Δ4-pregnene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6α-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6β-methyl-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6-methyl-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6-methyl-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-methylaminomethyl-6α-fluoro-Δ4-pregnene-17α-ol-3,20-dione
21-methylaminomethyl-6α-fluoro-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-methylaminomethyl-6-fluoro-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-methylaminomethyl-6-fluoro-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-aminomethyl-6α-fluoro-Δ4-pregnene-17α-ol-3,20-dione
21-aminomethyl-6α-fluoro-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-aminomethyl-6-fluoro-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-aminomethyl-6-fluoro-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-butylaminomethyl-6α-fluoro-Δ4-pregnene-17α-ol-3,20-dione
21-butylaminomethyl-6α-fluoro-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-butylaminomethyl-6-fluoro-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-butylaminomethyl-6-fluoro-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-dipropylaminomethyl-6α-fluoro-Δ4-pregnene-17α-ol-3,20-dione
21-dipropylaminomethyl-6α-fluoro-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-dipropylaminomethyl-6-fluoro-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-dipropylaminomethyl-6-fluoro-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6α-fluoro-Δ4-pregnene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6α-fluoro-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6-fluoro-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6-fluoro-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6α-fluoro-Δ4-pregnene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6α-fluoro-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6-fluoro-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6-fluoro-Δ1,4,6-pregnatriene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6α-fluoro-Δ4-pregnene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6α-fluoro-Δ1,4-pregnadiene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6-fluoro-Δ4,6-pregnadiene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6-fluoro-Δ1,4,6-pregnatriene-17α-ol-3,20-dione

EXAMPLE XLV

21-Diethylaminomethyl-Δ1,4-Pregnadiene-3,20-Dione

A total of 35 grams of Δ1,4-pregnadiene-3,20-dione was taken up in 500 ml. of n-amyl alcohol containing 20 grams of paraformaldehyde, 60 grams of diethylamine hydrochloride and 2 ml. of dilute hydrochloric acid. The mixture was refluxed for 2 hours and filtered. The residue was digested with 150 ml. of hot 0.25 N hydrochloric acid and filtered. The filtrate was adjusted to a pH value of approximately 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 removing the solvent in vacuo.

The procedure was repeated using the appropriate starting material to prepare the following compounds:

21-diethylaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-diethylaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-diethylaminomethyl-6α-fluoro-$\Delta^{1,4}$pregnadiene-3,20-dione
21-diethylaminomethyl-6α-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-diethylaminomethyl-6β-methyl-$\Delta^{1,4}$-pregnadiene-3,20-dione
21-diethylaminomethyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-diethylaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-diethylaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-diethylaminomethyl-6-fluoro-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-diethylaminomethyl-6-methyl-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-diethylaminomethyl-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-diethylaminomethyl-6α-chloro-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-diethylaminomethyl-6α-bromo-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-diethylaminomethyl-6α-fluoro-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-diethylaminomethyl-6α-methyl-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-diethylaminomethyl-6β-methyl-$\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione
21-diethylaminomethyl-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-diethylaminomethyl-6-chloro-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-diethylaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-diethylaminomethyl-6-fluoro-$\Delta^{1,4,6}$-pregnatriene-17α-3,20-dione
21-diethylaminomethyl-6-methyl-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione

EXAMPLE XLVI

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

A total of 50 grams of $\Delta^{1,4}$-pregnadiene-17α-ol-3,20-dione was taken up in 750 ml. of N-propanol containing 24 grams of paraldehyde, 80 grams 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 10% sodium carbonate. The solution was extracted with chloroform, the chloroform solution dried over anhydrous sodium sulfate, filtered and evaporated in vacuo to leave the desired product as a residue.

EXAMPLE XLVII

21-Dipropylaminomethyl-6-Fluoro-$\Delta^{1,4,6}$-Pregnatriene-17α-Ol-3,20-Dione

A total of 10 grams of 6-fluoro-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione was taken up in 500 ml. of N-butanol containing 4.8 grams of paraldehyde, 16 grams of dipropylamine hydrochloride and 15 drops of 3 N hydrochloric acid. The solution was refluxed under nitrogen for 4 hours during which time an additional portion 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 and the pH of the filtrate adjusted to approximately 10 with 10% aqueous sodium carbonate. The mixture was extracted with benzene, the organic layer dried over anhydrous sodium sulfate, filtered and the desired product recovered by removing the solvent in vacuo.

EXAMPLE XLVIII

A variety of 17-esters of the free alcohols prepared as described in the previous examples were each prepared by acylation using conventional methods. With compounds in which either R_1 or R_2 or both are hydrogen, the esters are prepared from the corresponding 21-methylene compounds before reaction with the base. The compounds prepared include formates, propanoates, propenoates, isobutyrates, hexanoates, benzoates, octanoates, decanoates, trimethyl acetates, cyclopentylpropionates, etc.

EXAMPLE XLIX

A variety of pharmaceutically acceptable acid addition salts of the amines prepared as described in the previous examples were each prepared using the standard methods. Those prepared include acid addition salts of the following acids: hydrochloric, hydrobromic, hydriodic, sulfuric, succinic, maleic, tartaric, citric and glycolic.

EXAMPLE L

Preparation of Quaternary Ammonium Compounds

The following procedures are illustrative of the methods used to prepare the quaternary ammonium halides of this invention. A solution of 7.5 grams of 21-dibutylaminomethyl-Δ^4-pregnene-17α-ol-3,20-dione 17-acetate in 180 ml. of methanol containing 80 ml. of methylbromide was allowed to stand overnight and the mixture was then evaporated to dryness in vacuo. The residue was triturated with acetone and the desired product recovered by filtration. An additional crop of the quaternary compound was obtained by evaporation of the acetone filtrate and this was purified by trituration with methanol and recovered by filtration.

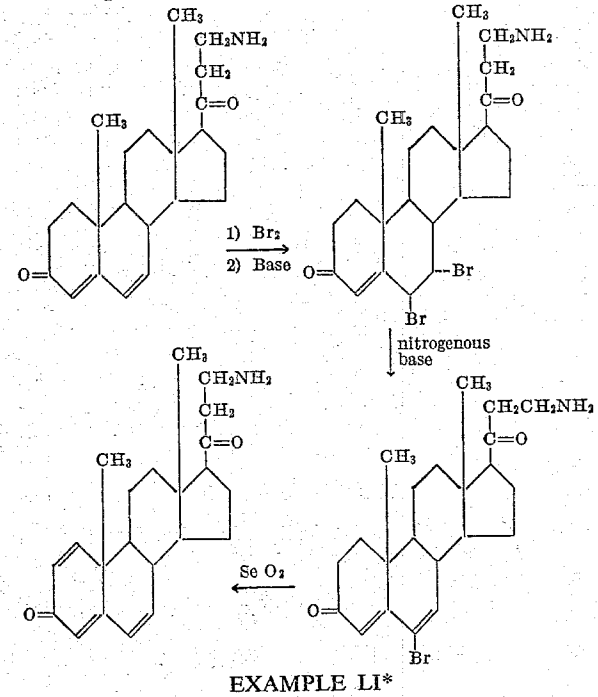
A solution of 7.5 grams of 21-aminomethyl-6-fluoro-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione in 150 ml. of ethanol containing a 50% molar excess of butyl chloride was allowed to stand at 25° C. for 16 hours and the mixture was evaporated to dryness in vacuo. The residue was triturated with acetone and the desired product recovered by filtration.

A solution of 8 grams of 21-dipropylaminomethyl-$\Delta^{1,4}$-pregnadiene-3,20-dione in 200 ml. of methanol containing a 20% molar excess of methyl iodide was allowed to stand for 20 hours at approximately 28° C. The mixture was then evaporated to dryness. The residue was triturated with ether and the desired product recovered by filtration.

Other quaternary alkyl ammonium fluorides, chlorides, bromides and iodides within the scope of this invention were prepared in accordance with the procedure of this example.

The preparation of Δ^6-6-bromo compounds within the purview of this invention presents special problems because of the tendency of the bromine atom to split out during the quinone dehydration. These compounds, however, can be readily prepared by preparing a 21-aminomethyl-$\Delta^{4,6}$-compound which is then dibrominated with a slight molar excess of bromine and dehydrobrominated at the 6,7-position with nitrogenous base. The following sequence illustrates this series of reactions with 21-aminomethyl-$\Delta^{4,6}$-pregnadiene-3,20-dione. It is equally applicable with other 6-desbromo compounds of this invention.

A double bond may be introduced at the 1,2-position of the final product using selenium dioxide if desired.



EXAMPLE LI*

21-Aminomethyl-6β,7α-Dibromo-Δ⁴-Pregnene-3,20-Dione

A total of 5 grams of 21-aminomethyl-$\Delta^{4,6}$-pregnadiene-3,20-dione was taken up in 100 ml. of dioxane. A 10% molar excess of bromine in propionic acid was added at 20° C. to 30° C. and the mixture maintained at this temperature for five hours. The solution was neutralized by the careful addition of 5% aqueous sodium bicarbonate solution, and the dioxane removed in vacuo. The mixture was extracted with ethylene chloride, the organic layer dried over anhydrous sodium sulfate, filtered and the desired product recovered by removal of the solvent in vacuo.

EXAMPLE LII

21-Aminomethyl-6-Bromo-$\Delta^{4,6}$-Pregnadiene-3,20-Dione

The product from the previous example was taken up in 100 ml. of collidine and refluxed for 3 hours. An equal volume of water was added and the mixture neutralized by the cautious addition of 5% aqueous hydrochloric acid. It was then extracted with chloroform and the desired product recovered by removing the chloroform in vacuo after drying over anhydrous sodium sulfate.

EXAMPLE LIII

21-Aminomethyl-6-Bromo-$\Delta^{1,4,6}$-Pregnatriene-3,20-Dione

This compound was prepared from the product of the previous example using the procedure of Example V.

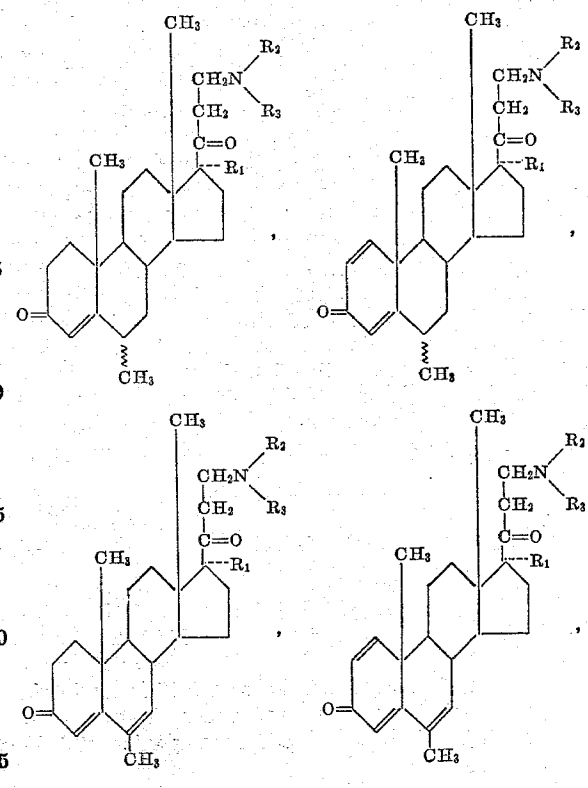
The following compounds were prepared using the procedures of Examples LI, LII and LIII. Acid addition salts, 17-esters and quaternary compounds were prepared in accordance with the procedures of Examples XLVIII, XLIX and L.

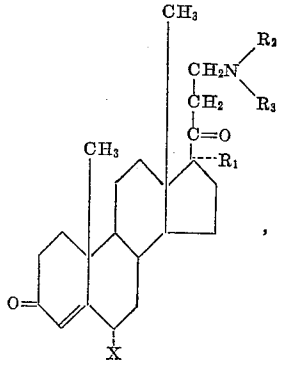
21-methylamino-6-bromo-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-methylaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-aminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-aminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-butylaminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-butylaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-dipropylaminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-dipropylaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-3,20-dione

21-pyrrolidinoaminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-pyrrolidinoaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-piperidinoaminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-piperidinoaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-morpholinoaminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-3,20-dione
21-morpholinoaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-3,20-dione
21-methylaminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-methylaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-aminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-aminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-butylaminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-butylaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-dipropylaminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-dipropylaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-pyrrolidinoaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-piperidinoaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6-bromo-$\Delta^{4,6}$-pregnadiene-17α-ol-3,20-dione
21-morpholinoaminomethyl-6-bromo-$\Delta^{1,4,6}$-pregnatriene-17α-ol-3,20-dione

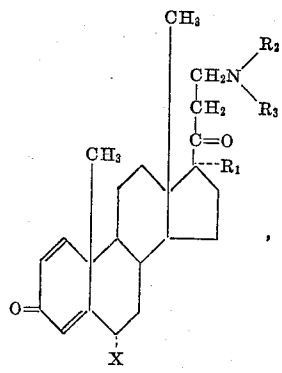
What is claimed is:

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

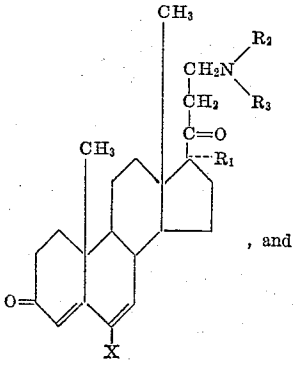




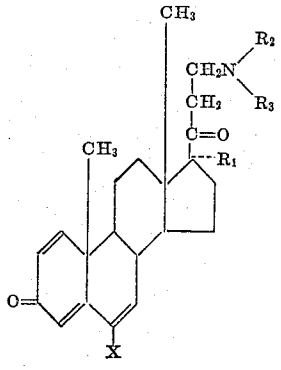
,



,



, and



wherein X is selected from the group consisting of hydrogen, fluorine, chlorine and bromine; R_1 is selected from the group consisting of hydrogen, hydroxyl, and acylated hydroxyl wherein the acyl group is derived from a monocarboxylic acid containing only carbon, hydrogen and oxygen up to a total of ten carbon atoms; R_2 and R_3 are selected from the group consisting of hydrogen and alkyl containing up to four carbon atoms and further groups wherein R_2 and R_3 are joined and together with the nitrogen atom to which they are joined form a heterocyclic ring selected from the group consisting of pyrrolidine, piperidine and morpholine; pharmaceutically acceptable acid addition derivatives thereof; and quaternary alkyl ammonium halide derivatives thereof wherein the alkyl group contains up to four carbon atoms, R_2 and R_3 always being other than hydrogen in the said quaternary alkyl ammonium halide derivatives.

2. A pharmaceutical composition comprising a compound as claimed in claim 1 and a pharmaceutically acceptable carrier.

No references cited.