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REDUCTION OF STEROID KETONES WITH ALKALI METAL BOROHYDRIDE

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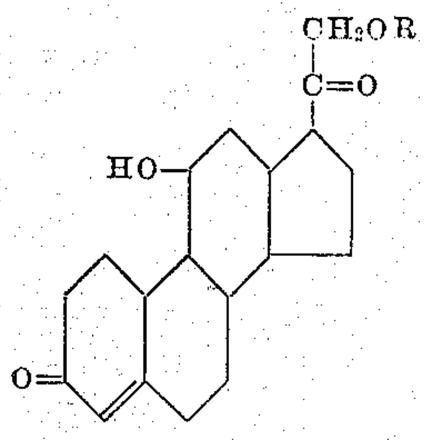
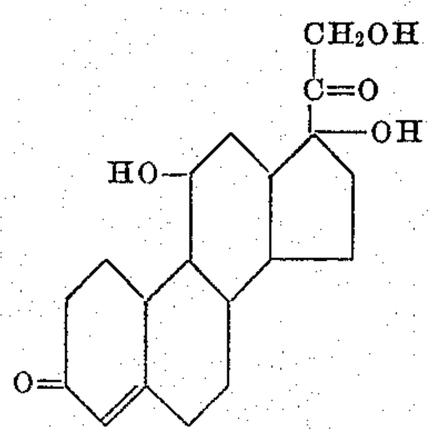
This invention is concerned generally with the selective reduction of ketone groupings to hydroxy radicals in steroid compounds containing other reducible linkages. More particularly, it relates to a novel process for selectively reducing 11 - keto - cyclopentanopolyhydrophenanthrene compounds containing at least one unsaturated carbon-nitrogen linkage to form the corresponding 11 - hydroxy - cyclopentanopolyhydrophenanthrene compounds without affecting the carbon-nitrogen linkage. This selective reduction procedure is especially valuable in the synthesis of 11-hydroxy-pregnene compounds such as the adrenal hormones, corticosterone and 17-hydroxy-corticosterone, which may be chemically represented as follows:



Corticosterone



17-hydroxy-corticosterone

The configuration of the 11-hydroxyl substituent in such naturally-occurring steroids, which has been found to correspond to that of the two angular methyl groups and the side chain of the steroid molecule, is conventionally designated β and written above the plane of the ring system, i. e. a full line in the formulae.

Heretofore, the synthesis of cortical steroids hydroxylated at position 11 has encountered an apparently insurmountable obstacle by virtue of the following chemical facts: (1) The polyfunctional character of this class of steroids and the fact that such cortical steroids ordinarily possess additional keto substituents in the 3 and/or 20-positions; (2) the extremely low reactivity (ascribed to steric hinderance) of the 11-keto substituent; (3) the known susceptibility of the β-hydroxyl group at position 11 to oxidation and elimination reactions, together with the seemingly anomalous inertness of the 11(β)-hydroxyl to acylating agents.

Thus, when 11-keto-10,13-cyclopentanopolyhydrophenanthrenes containing additional keto substituents (for example in the 3 and/or 20-positions) are reduced using conventional methods of hydrogenation or chemical reduction, it has been found that reduction of the keto

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radicals in the 3 and 20-positions takes place preferentially to reduction of the 11-ketone. Only by employing relatively drastic reduction conditions, is it possible to reduce the 11-keto substituent and, under such drastic conditions of reduction, the 3 and 20-keto groups are likewise reduced. The compounds thus obtained, in attempted syntheses of cortical steroids, are 10,13 - dimethyl - cyclopentanopolyhydrophenanthrenes containing an 11(β)-hydroxy radical, and additional hydroxy radicals in the 3 and/or 20-positions of the molecule. Attempts to preferentially oxidize the 3 and/or 20-hydroxy radicals to the corresponding keto substituents, while retaining the β-hydroxyl radical attached to the 11-carbon atom, have not been successful due to the comparatively high susceptibility of the 11(β)-hydroxy grouping to oxidation. Anomalously, it has not been possible to "protect" the 11(β)-hydroxy group by acylation, while leaving the 3 and/or 20-hydroxy radicals free to be oxidized, since the 11(β)-hydroxyl group is subject to very pronounced steric hindrance and has resisted acylation by all methods tried. (See page 408 of the text "Natural Products Related to Phenanthrene" by Fieser and Fieser, 3rd edition, Rheinhold Publishing Corp., New York, 1949.)

It was known previously that, when 11-keto-10,13 - dimethyl - cyclopentanopolyhydrophenanthrene compounds containing additional keto groupings in the 3 and/or 20-positions were reacted with the usual ketone reagents, such as hydroxylamine, semicarbazide, arylhydrazines, hydrogen cyanide, ethyl orthoformate, and the like, the ketone groupings in the 3 and/or 20-positions reacted leaving the 11-keto radical unchanged. It was thus known heretofore how to prepare 11-keto-10,13-diamethylcyclopentanopolyhydrophenanthrenes containing in the 3 and/or 20-positions various substituents hydrolyzable to keto radicals and containing unsaturated carbon-nitrogen linkages, such as oximino, semicarbazido, arylhydrazino and cyanhydrin groupings. In the case of the 11-keto-10,13-dimethyl - cyclopentanopolyhydrophenanthrenes containing a 20-cyanhydrin grouping, it was also known that these compounds could be reacted with a dehydrating agent to produce the corresponding Δ^{17} - 20 - cyano - 11 - keto - 10,13-dimethyl - cyclopentanopolyhydrophenanthrenes. These Δ^{17} - 20 - cyano - 11 - keto - 10,13 - dimethyl - cyclopentanopolyhydrophenanthrenes are key intermediates in the preparation of adrenal hormones containing a 17-hydroxy sub-

stituent since they can be readily converted, by reaction with an oxidizing agent followed by a hydrolyzing agent, to the corresponding 17-hydroxy - 20 - keto - 10,13 - dimethyl - cyclopentanopolyhydrophenanthrene compounds.

These 11 - keto-10,13-cyclopentanopolyhydrophenanthrenes containing, in place of the ketone grouping in the 3 and/or 20-positions, a grouping containing an unsaturated carbon-nitrogen linkage, were not previously considered to be of any use whatsoever as intermediates for the synthesis of 11-hydroxy-10,13-dimethyl-cyclopentanopolyhydrophenanthrenes containing 3 and/or 20-keto groupings. This was due to the fact that no method was known whereby the 11-keto group in such 11-keto - 10,13 - dimethyl-cyclopentanopolyhydrophenanthrene compounds could be reduced without, at the same time, reducing the unsaturated carbon-nitrogen linkages. For example, ordinary methods of hydrogenation or chemical reduction drastic enough to reduce the 11-keto-groupings in such compounds, invariably also reduced the carbon-nitrogen linkages in the 3 and/or 20 substitutents. The object of the present invention, therefore, was to accomplish this selective reduction operation and thus make possible the preparation of cortical steroids hydroxylated at position 11.

We have now discovered that this selective reduction of the 11-keto substitutent in 11-keto-10,13 - dimethyl - cyclopentanopolyhydrophenanthrene compounds containing at least one unsaturated carbon-nitrogen linkage can be achieved by reacting said 11-keto compound, in the presence of a diluent, with an alkali metal borohydride, such as lithium borohydride, sodium borohydride, and the like. The alkali metal borohydrides, while being sufficiently reactive to reduce the substantially unreactive 11-keto substituent, do not have any appreciable reducing effect on unsaturated carbon-nitrogen linkages present in the steroid molecule. This remarkable selective action (with respect to unsaturated groupings in steroid compounds) shown by alkali metal borohydrides is indeed surprising in view of the fact that the closely related reducing agent, lithium aluminum hydride, does not possess this selective action. When an 11-keto-10,13-dimethyl-cyclopentanopolyhydrophenanthrene containing an unsaturated carbon-nitrogen linkage is reacted with lithium aluminum hydride the carbon-nitrogen linkage is reduced along with the 11-ketone grouping.

We employ as starting materials in our novel process 11-keto - 10,13 - cyclopentanopolyhydrophenanthrenes containing at least one unsaturated carbon-nitrogen linkage as for example, oximino, semicarbazido, or arylhydrazino-substituted 11-keto - 10,13 - dimethyl-cyclopentanopolyhydrophenanthrenes such as 3-(oximino, semicarbazido, or arylhydrazino)-11,20-diketo-pregnane; 3,11-diketo-20-(oximino, semicarbazido or arylhydrazino)-pregnane; 3-hydroxy-11-keto-20-(oximino, semicarbazido or arylhydrazino)-pregnane; 3,20-(dioximino, disemicarbazido or diarylhydrazino)-11-keto-pregnane; 3-(oximino, semicarbazido or arylhydrazino)-11,20-diketo-21-hydroxy-pregnane; 3,21-dihydroxy-11-keto-20-(oximino, semicarbazido or arylhydrazino)-pregnane; 3,11-diketo-20-(oximino, semicarbazido or arylhydrazino)-21-hydroxy-pregnane; 3-(oximino, semicarbazido or arylhydrazino)-11,20-diketo - 21 - acyloxy-pregnane; 3,11-diketo-20-(oximino, semicarbazido or arylhydrazino)-21-acyloxy-pregnane; 3,20-(dioximino, disemicarbazido or diarylhydrazino)-11-keto-21-acyloxy-pregnane; 3-hydroxy-11-keto-20-(oximino, semicarbazido or arylhydrazino) - 21 - acyloxy-pregnane, Δ^4-3,20-(dioximino, disemicarbazido or diarylhydrazino)-11-keto-21-hydroxy - pregnene, Δ^4-3,20-(dioximino, disemicarbazido or diarylhydrazino)-11-keto-21-acyloxy-pregnene, and the like. Instead of "protecting" auxiliary keto radicals by conversion to the oximes, semicarbazones or arylhydrazones (the substitutents having unsaturated carbon-nitrogen linkages in the illustrative examples set forth hereinabove), these keto radicals can be converted by reaction with hydrogen cyanide to the corresponding cyanhydrin such as 3,20-dihydroxy-11-keto-20-cyano-pregnane; 3,20-dihydroxy-11-keto-20-cyano-21-acyloxy - pregnane; 3,20,21-trihydroxy-11-keto-20-cyano - pregnane; 3,21-diacyloxy-11-keto-20-hydroxy-20-cyano-pregnane; and the like.

We particularly prefer to employ, as starting materials in our procedure, 11-keto-10,13-cyclopentanopolyhydrophenanthrene compounds containing a Δ^{17} unsaturated linkage and a cyano radical attached to the C-20 carbon atom such as Δ^{17}-11-keto-20-cyano-pregnene; Δ^{17}-3,11-diketo-20-cyano-pregnene; Δ^{17}-3-hydroxy-11-keto-20-cyano-pregnene; Δ^{17}-3,11-diketo-20-cyano-21-hydroxy - pregnene; Δ^{17}-3,21-dihydroxy-11-keto-20-cyano-pregnene; Δ^{17} - 3 - hydroxy-11-keto-20-cyano-21-acyloxy - pregnene, Δ^{17}-3,11-diketo-20-cyano-21-acetoxy - pregnene; Δ^{17}-3,11-diketo-20-cyano-21-acyloxy-pregnenes, as well as Δ^{17}-11-keto-20-cyano-10,13-dimethyl-cyclopentanopolyhydrophenanthrene compounds containing additional unsaturated carbon nitrogen linkages such as Δ^{17}-3-(oximino, semicarbazido or arylhydrazino)-11-keto-20-cyano-pregnene; Δ^{17}-3-(oximino, semicarbazido or arylhydrazino)-11-keto-20-cyano - 21 - hydroxy - pregnene; Δ^{17}-3-(oximino, semicarbazido or arylhydrazino)-11-keto-20-cyano-21-acyloxy-pregnene, and the like.

It will be noted that the starting materials described in the preceding paragraph include Δ^{17}-11-keto-20-cyano-pregnene compounds in which a keto grouping in the 3-position has been "protected" by conversion to an oximino, semicarbazido or aryl-hydrazino grouping. It is an important embodiment of our invention that Δ^{17}-11-keto-20-cyano-pregnenes containing a 3-keto-substituent can be protected by forming the corresponding ketal, that is the Δ^{17}-3,3-dialkoxy-11-keto-20-cyano-pregnene compound, such as Δ^{17}-3,3-dimethoxy-11-keto-20-cyano-pregnene; Δ^{17}-3,3-diethoxy-11-keto-20-cyano-21-hydroxy-pregnene; Δ^{17}-3,3-diethoxy - 11 - keto - 20 - cyano-21-acyloxy-pregnene, and the like. These compounds, which contain an unsaturated carbon-nitrogen linkage (the 20-cyano group) and a ketal group can also be utilized as starting materials in carrying out our invention.

In carrying out our novel process, the 11-keto-10,13 - dimethyl - cyclopentanopolyhydrophenanthrene compound containing at least one unsaturated carbon-nitrogen linkage, is reacted with an alkali metal borohydride, such as lithium borohydride, sodium borohydride, and the like. The reaction is ordinarily conducted in the presence of a diluent, preferably in the presence of a solvent such as tetrahydrofuran, dimethyl formamide, diethyl ether, and the like. It is ordinarily preferred to carry out the reaction by adding a tetrahydrofuran solution of the 11-keto-10,13 - dimethyl - cyclopentanopolyhydrophenanthrene compound containing at least one unsaturated carbon-nitrogen linkage to a tetrahydro-

furan solution of the alkali metal borohydride reducing agent. This addition of the 11-keto-steroid compound to the reducing agent is preferably conducted portionwise, while maintaining the temperature of the reaction mixture at approximately 25° C. However, with the more active alkali metal borohydride (lithium borohydride), the reaction can be carried out at a lower temperature with lengthening of the reaction time. Conversely, with the less active sodium borohydride, a higher temperature may be necessary, it ordinarily being preferred to conduct the reaction, when using sodium borohydride as the reducing agent, at temperatures of about 60–70° C.

Although the preferred solvent for carrying out the reaction is tetrahydrofuran, it is sometimes preferred to utilize dimethylformamide as the solvent, in view of the fact that this liquid is an excellent solvent for many steroid compounds which are difficultly soluble in other solvents. In this connection, it should be pointed out that dimethylformamide is ordinarily reduced by active reducing agents; the fact that it is not affected by alkali metal borohydrides makes possible its employment as a solvent in this reduction operation.

Although it is ordinarily preferred to maintain the reaction temperature at about 25° C., somewhat lower temperatures down to 0° C. when using lithium borohydride, as well as higher temperatures up to 70° C., when using sodium borohydride, can be employed. When the reaction is carried out with lithium borohydride at the preferred temperature of about 25° C., the reaction is ordinarily substantially complete in less than approximately one hour. When the reaction is carried out with sodium borohydride at the preferred temperature of about 65° C., the reaction is substantially complete in less than 24 hours.

After completion of the reaction, the resulting 11(β-hydroxy-10,13-dimethyl-cyclopentanopolyhydrophenanthrene compound (in which the unsaturated carbon-nitrogen linkages are identical with those present in the starting material) is recovered from the reaction mixture by conventional means. This is ordinarily accomplished by cautiously acidifying the reaction mixture, preferably utilizing aqueous acetic acid, thereby decomposing excess alkali metal borohydride. The 11(β)-hydroxy substituted steroid compounds can then be recovered by evaporating the reaction mixture to a small volume, preferably in vacuo and diluting the concentrate with water. The product which separates, frequently in the form of an oil, can then be extracted from this aqueous mixture utilizing conventional water-immiscible solvents such as benzene, ether, chloroform, ethyl acetate, and the like. The extract of 11(β)-hydroxy-steroid is then purified by conventional means, as for example, by washing successively with water and dilute aqueous alkaline solution, followed by drying. The product is recovered from the extract by evaporating the solvent therefrom, and can be further purified by recrystallization from solvents such as aqueous acetone, benzene, and the like. Where recrystallization from an organic solvent alone is insufficient to accomplish purification, it has been found convenient to subject the extract to a preliminary chromatographic fractionation utilizing activated alumina as the adsorbent.

The following examples illustrate methods of carrying out the present invention, but it is to

be understood that these examples are given for purposes of illustration and not of limitation.

Example 1

A mixture of 35.5 g. of Δ^{17}-3,11-diketo-21-hydroxy-20-cyano-pregnene, 22.2 g. of ethyl orthoformate, 0.69 g. of absolute ethyl alcohol, 200 ml. of sodium-dried benzene and 10 drops of concentrated sulfuric acid was heated with occasional agitation at a temperature of 70–75° C. for a period of approximately 2 hours. The resulting light-brown benzene reaction solution was cooled to room temperature and 5 g. of solid sodium bicarbonate was added followed by 150 ml. of a 5% aqueous solution of sodium bicarbonate. The mixture was shaken vigorously, and the aqueous layer was separated from the benzene solution. The aqueous layer was then extracted with two 85 ml. portions of ether, and the ether extracts were combined with the benzene solution. The combined benzene-ether solution was washed with two 100 ml. portions of water, and one 100 ml. portion of saturated aqueous sodium chloride solution and then dried over 10 g. of anhydrous magnesium sulfate. The solvents were then evaporated in vacuo from the dry benzene-ether solution to give 45.5 g. of Δ^{17}-3,3-diethoxy-11-keto-20-cyano-21-hydroxy-pregnene, which was obtained in the form of a fluffy, pale-yellow, amorphous solid; the infra-red absorption spectrum (chloroform solution) showed the principal bands at 2.85 mμ (—OH), 4.57 mμ (—C≡N), 5.83 mμ (>C=O), 6.08 mμ (>C=C<) and

$$9.18\text{m}\mu\left(\diagdown\!\!\diagup\text{C—O—}\right)$$

the ultraviolet absorption spectrum exhibited

$$\lambda_{\text{max.}}^{\text{CH}_3\text{OH}}\ 2230\ \text{Å.},\ E_{1\text{ cm.}}^{1\%}\ 364$$

45 g. of Δ^{17}-3,3-diethoxy-11-keto-20-cyano-21-hydroxy-pregnene, obtained as described hereinabove, was dissolved in 300 ml. of dry tetrahydrofuran (dried over metallic sodium) and this solution was added, dropwise, with agitation over a ½ hour period, to a solution of 9.7 g. of lithium borohydride in 300 ml. of dry tetrahydrofuran, while maintaining the temperature of the mixture at approximately 25° C. The resulting mixture was stirred for an additional period of 20 minutes at a temperature of 25° C., and was then cooled and stirred for 10 minutes at about 5° C. 600 ml. of aqueous acetic acid containing 120 ml. of glacial acetic acid was added cautiously, with stirring, to the resulting mixture whereupon a vigorous evolution of gas occurred. The resulting mixture was evaporated in vacuo to a volume of approximately 600 ml., and the concentrated solution was then diluted with approximately 600 ml. of water. The oily organic layer which separated was then extracted from the mixture utilizing 600 ml. of a 5:1 benzene-ether mixture followed by two 200 ml. portions of benzene. The combined benzene-ether extracts were washed with two 200 ml. portions of water, one 200 ml. portion of 5% aqueous sodium bicarbonate solution, and one 200 ml. portion of saturated aqueous sodium chloride solution. The washed benzene-ether extract was then dried over 30 g. of anhydrous magnesium sulfate, the dry solution was filtered, and the solvents were evaporated therefrom in vacuo to give 40.1 g. of crude Δ^{17}-3,3-diethoxy-11,21-dihydroxy-20-cyano-pregnene which was obtained in the form of a fluffy, pale-yellow, amorphous solid.

40.1 g. of crude Δ^{17}-3,3-diethoxy - 11,21 - dihydroxy-20-cyano-pregnene, prepared as described hereinabove, was dissolved in a mixture of 425 ml. of acetone and 55 ml. of water. To this solution was added 4.0 ml. of 2.5 N aqueous hydrochloric acid, and the resulting solution was allowed to stand at room temperature for a period of about 30 hours. 25 ml. of 5% aqueous sodium bicarbonate solution was then added to the reaction mixture, and the resulting solution was evaporated in vacuo to a small volume, thereby evaporating substantially all of the acetone present in the solution; during this evaporation, a pale-yellow oil separated. The residual material was diluted with 800 ml. of water, and the oily organic material was extracted from the aqueous mixture utilizing one 400 ml. portion and two 300 ml. portions of chloroform. The combined chloroform extracts were washed successively with one 300 ml. portion of 5% aqueous sodium bicarbonate solution, one 300 ml. portion of water, and the washed chloroform extracts were then dried over 15 g. of anhydrous magnesium sulfate. The dry chloroform solution was filtered and the chloroform evaporated in vacuo to give 38.8 g. of crude Δ^{17}-3-keto-11,21-dihydroxy-20-cyano-pregnene which was obtained in the form of a pale, buff-colored, partly crystalline solid. This crude material, after one recrystallization from aqueous acetone, gave 15.3 g. of substantially pure Δ^{17}-3-keto-11,21-dihydroxy-20 - cyano - pregnene which was obtained in the form of colorless needles; M. P. 216.5–218.5° C. (melted partly at 206° C. then resolidified). An analytically pure sample obtained by several recrystallizations from aqueous acetone melted at 217.5–221.5° C. (melted partly at 207–210° C., then solidified); $[\alpha]_D = +24.4°$ (1.03 in acetone);

$$\lambda_{max.}^{CH_3OH}\ 2230\ \text{Å.},\ E_{1\ cm.}^{1\%}\ 387$$

Analysis calc'd for $C_{22}H_{31}O_3N$: C, 73.91; H, 8.74. Found: C, 74.12; H, 8.73.

Example 2

Twenty grams of Δ^{17}-3,11-diketo-20-cyano-21-hydroxy-pregnene was dissolved in 300 ml. of glacial acetic acid and to this solution was added a solution containing 12.55 g. of semicarbazide hydrochloride and 12.55 g. of anhydrous sodium acetate dissolved in 28 ml. of water and 28 ml. of glacial acetic acid; the latter solution was rinsed into the reaction mixture with an additional 44 ml. of glacial acetic acid. The resulting mixture was heated to a temperature of 65–70° C. for a period of approximately 2½ hours during which time a small amount of crystalline material separated. The resulting suspension was evaporated in vacuo to a thick slurry of crystalline solid, and 200 ml. of water was added to said slurry. The resulting aqueous mixture was agitated vigorously to suspend caked material, the slurry was then filtered and the crystalline product washed twice with water to give 24.2 g. of colorless needles which melted at 225–230° C. with evolution of gas. One recrystallization of this product from methanolchloroform afforded 20.2 g. of substantially pure Δ^{17}-3 - semicarbazido-11-keto-20-cyano-21-hydroxy-pregnene; M. P. 238–240° C. (vigorous evolution of gas). This product was further purified by repeated recrystallization from methanol-chloroform and the product dried at 140° C. to give analytically pure Δ^{17}-3-semicarbazido-11-keto - 20 - cyano - 21 - hydroxy-pregnene; M. P. 244–245° C. (evolution of gas). Analysis calc'd for $C_{23}H_{32}O_3N_4$: N, 13.58, Found: N, 13.47.

Example 3

12.36 g. of Δ^{17}-3-semicarbazido - 11 - keto - 20 - cyano-21-hydroxy-pregnene (M. P. 238–240° C.) was dissolved in 1500 ml. of dry tetrahydrofuran (dried over metallic sodium), and this solution was added with stirring, over a period of approximately ½ hour, to a solution of 4.36 g. of lithium borohydride in 200 ml. of dry tetrahydrofuran, while maintaining the temperature of the mixture at approximately 25° C. The resulting mixture was stirred for an additional period of 20 minutes at a temperature of 25° C., and was then cooled and stirred for 10 minutes at about 5° C. 450 ml. of aqueous acetic acid containing 51.5 ml. of glacial acetic acid was then added cautiously, with stirring, to the resulting mixture, and the clear, colorless reaction mixture was evaporated in vacuo under a nitrogen atmosphere to a volume of approximately 400 ml. The colorless oily organic material which separated was extracted from the mixture utilizing one 350 ml. portion of chloroform and two 150 ml. portions of chloroform. The combined chloroform extracts were washed with two 250 ml. portions of water and with one 200 ml. portion of 5% aqueous sodium bicarbonate solution, and the washed chloroform extracts were dried over 10 g. of anhydrous sodium sulfate. The dry chloroform solution was then filtered and the chloroform evaporated to give 11.5 g. of crude Δ^{17}-3-semicarbazido-11,21-dihydroxy - 20 - cyano-pregnene which was obtained in the form of a gummy, buff-colored solid.

4.5 g. of this material was mixed with 15 ml. of glacial acetic acid, 7.5 ml. of water, 9.05 g. of anhydrous sodium acetate and 9.0 ml. of 90% pyruvic acid, and the mixture was heated at a temperature of 80° C. in an atmosphere of nitrogen for a period of about 3 hours. The reaction mixture was cooled to room temperature, an additional 0.9 ml. of 90% pyruvic acid was added thereto, and the resulting mixture was heated under nitrogen at a temperature of 80° C. for an additional one-hour period. The resulting mixture was allowed to stand overnight at room temperature whereupon a considerable quantity of crystalline material separated. 180 ml. of water was added to this mixture, and the organic material was extracted therefrom utilizing one 80 ml. portion and three 35 ml. portions of chloroform. The combined chloroform extracts were washed with two 50 ml. portions of water, two 50 ml. portions of 5% aqueous sodium bicarbonate solution, again with 50 ml. of water, and the washed chloroform solution was then dried over 5 g. of anhydrous magnesium sulfate. The dry chloroform solution was then filtered and the solvent was evaporated from the filtrate in vacuo to give 4.25 g. of partly crystalline, light, buff-colored material. This product, after one recrystallization from acetone, afforded 1.75 g. of substantially pure Δ^{17}-3-keto-11,21-dihydroxy-20-cyano-pregnene; which was obtained in the form of colorless needles; M. P. 216.5–219.5° C. (melted partly at 206.5° C. to 208° C. then resolidified); there was no depression in melting point when this material was admixed with Δ^{17}-3-keto-11,21-dihydroxy-20-cyano-pregnene as prepared via the 3-diethyl ketal as described in Example 1 hereinabove.

Example 4

1.07 g. of Δ^{17}-3,11-diketo-21-hydroxy-20-cyano-pregnene was dissolved in 23 ml. of dry tet-

rahydrofuran (dried over metallic sodium) and this solution was added, dropwise, with stirring, over a 10 minute period, to an ice-cold solution of 0.15 g. of lithium borohydride in 6 ml. of dry tetrahydrofuran. The solution of the diketone was rinsed into the solution containing lithium borohydride by means of an additional 2 ml. of dry tetrahydrofuran, and the resulting mixture was then stirred for an additional period of 20 minutes while maintaining the temperature at approximately 0° C. 20 ml. of water was then added dropwise to the cold reaction mixture, followed by the cautious addition of 2 ml. of glacial acetic acid. The resulting mixture was then stirred for a period of about 10 minutes, and the clear colorless reaction mixture was evaporated in vacuo to a volume of about 25 ml., whereupon a colorless oil separated. 25 ml. of ether was added to the oily mixture, and the resulting mixture was allowed to stand overnight whereupon a crystalline material separated from the mixture. The crystalline product was recovered from the water-ether mixture by filtration to give 0.5 g. of rosettes of colorless prisms which were further purified by a single recrystallization from acetone to give substantially pure Δ^{17}-3,21-dihydroxy-11-keto-20-cyano-pregnene; M. P. 251–257.5 C. (with slight previous softening); no depression in melting point was observed when this material was admixed with authentic Δ^{17}-3,21 - dihydroxy - 11 - keto - 20 - cyano - pregnene; comparative infrared spectra of this material and of the authentic specimen confirm its identity.

Example 5

5.35 g. of Δ^{17}-3,21-dihydroxy-11-keto-20-cyano-pregnene was dissolved in 100 ml. of dry tetrahydrofuran (dried over metallic sodium) and this solution was added, dropwise, with stirring, over a 30 minute period, to a solution of 1.45 g. of lithium borohydride in 75 ml. of dried tetrahydrofuran, while maintaining the temperature of the mixture at 25° C.; the solution of the pregnene compound was rinsed into the solution of lithium borohydride by means of an additional 25 ml. of tetrahydrofuran. The resulting mixture was stirred for an additional period of 30 minutes at a temperature of 25° C., and 100 ml. of 10% aqueous acetic acid solution was added cautiously, with stirring, to the mixture thereby decomposing the excess lithium borohydride. The resulting clear, colorless solution was evaporated in vacuo to a volume of approximately 100 ml., and the colorless oil which separated was extracted from the mixture utilizing three 50 ml. portions of ethyl acetate. The ethyl acetate extracts were combined and washed successively with one 30 ml. portion of water, and with one 30 ml. portion of a saturated solution of sodium chloride. The washed ethyl acetate solution was then dried over 5 g. of anhydrous magnesium sulfate, the dry solution was filtered, and the solvent evaporated from the filtered solution in vacuo to give a colorless amorphous solid. This material was crystallized from acetone-benzene to give 5.80 g. of substantially pure Δ^{17}-3,11(β),21-trihydroxy - 20 - cyano - pregnene which was obtained in the form of colorless, heavy needles containing two molecules of benzene of crystallization; M. P. 105–115° C. (with evolution of gas). The melting point was not raised by additional recrystallization of this material from acetone-benzene. Analysis calc'd for

$C_{22}H_{33}O_3N.2C_6H_6$

weight loss for $2C_6H_6$, 30.29. Found: weight loss on drying at 140° C., 29.98. Thus after drying at 140° C. there was obtained substantially pure, benzene - free Δ^{17} - 3,11,(β),21 - trihydroxy - 20-cyano-pregnene. Calc'd for $C_{22}H_{33}O_3N$: C, 73.50; H, 9.25; N, 3.90. Found: (dried at 140° C.) C, 74.11; H, 9.11; N, 3.91.

Example 6

0.5 g. of Δ^4-3,11,20–triketo-17,21-dihydroxy-pregnene, 0.483 g. of hydroxylamine hydrochloride and 0.57 g. of anhydrous sodium acetate were dissolved in 35 ml. of absolute ethyl alcohol and the resulting solution was heated at a temperature of 70° C. for a period of 3 hours. The resulting solution was evaporated in vacuo to a volume of approximately 10 ml., and 30 ml. of water was added to the concentrate thus obtained. The buff-colored oil which separated became crystalline upon trituration. The crystalline product was recovered by filtration, washed thoroughly with water, and dried to give 0.495 g. of crude Δ^4 - 3,20 - dioximino - 11 - keto - 17,21 - dihydroxy-pregnene; M. P. 184–187° C. dec. This product was further purified by repeated recrystallizations from methanol to give substantially pure Δ^4-3,20-dioximino-11-keto-17,21-dihydroxy-pregnene which was obtained in the form of colorless needles; M. P. 199–200° C. $[\alpha]_D$=+166° (1.0 in acetic acid);

$$\lambda_{max.}^{C_2H_5OH}\ 2400\ \text{Å.},\ E_{1\ cm.}^{1\%}\ 534$$

Analysis calc'd. for $C_{21}H_{30}O_5N_2$: C, 64.59; H, 7.74; N, 7.18. Found: C, 64.37; H, 7.83; N, 6.97.

Example 7

1.0 g. of Δ^4-3,20-dioximino-11-keto-17,21-dihydroxy-pregnene was dissolved in 15 ml. of dry tetrahydrofuran (dried over metallic sodium) and this solution was added, with stirring, over a period of approximately ½ hour, to a solution of 0.4 g. of lithium borohydride in 20 ml. of dry tetrahydrofuran, while maintaining the temperature of the mixture at approximately 25° C. The resulting mixture was stirred for an additional period of 40 minutes at a temperature of 25° C., and was then cooled to 5° C. 50 ml. of 10% aqueous acetic acid was added cautiously, with stirring, to the cold reaction mixture, and the resulting mixture was stirred for an additional 10 minutes. The clear colorless solution thus obtained was evaporated in vacuo to a small volume, and 30 ml. of water was added to the concentrated solution. The colorless solid which separated from the aqueous mixture was then recovered by filtration, washed thoroughly with water, and dried to give 0.93 g. of crude Δ^4-3,20-dioximino - 11,17,21 - trihydroxy - pregnene; this material did not melt at 310° C.

The crude product thus prepared was purified by precipitation from a saturated solution in methanol by the addition of water to give substantially pure Δ^4-3,20-dioximino-11,17,21-trihydroxy-pregnene, which was obtained in the form of a colorless powder which did not melt at 310° C.; $[\alpha]_D$=+150° (1.0 in acetic acid);

$$\lambda_{max.}^{C_2H_5OH}\ 2410\ \text{Å.},\ E_{1\ cm.}^{1\%}\ 453$$

Infrared absorption spectrum showed that the carbonyl bond was completely absent. Analysis calc'd for $C_{21}H_{32}O_5N_2$: C, 64.26; H, 8.22; N, 7.14. Found: C, 63.96; H, 7.59; N, 6.90.

Example 8

1.78 g. of Δ^{17}-3,11-diketo-20-cyano-21-hydroxy-pregnene was dissolved in 25 ml. of tetrahydrofuran containing 0.4 ml. of 2.5 N aqueous sodium hydroxide, and to this solution was added, all at once, a solution of 0.84 g. of sodium borohydride in 5.0 ml. of tetrahydrofuran, 5.0 ml. of water and 0.4 ml. of 2.5 N aqueous sodium hydroxide. The mixture was heated under reflux for a period of approximately twenty-four hours. The reaction mixture was then cooled to room temperature, and 35 ml. of 10% aqueous acetic acid was added to the cooled mixture thereby decomposing excess sodium borohydride.

The resulting clear, colorless solution was evaporated in vacuo to a small volume thereby substantially removing the tetrahydrofuran. The suspension of colorless oil thus obtained was diluted with 100 ml. of water and the oil was extracted from the aqueous mixture with three 50 ml. portions of ethyl acetate. The combined ethyl acetate extracts were washed successively with two 50 ml. portions of water, with two 50 ml. portions of 5% aqueous sodium bicarbonate solution, and with one 50 ml. portion of saturated aqueous sodium chloride solution. The washed ethyl acetate solution was dried over 5 g. of anhydrous magnesium sulfate, the solution was filtered and the solvent was evaporated therefrom in vacuo to give 1.92 g. of a colorless amorphous solid. This material was crystallized from acetone-benzene to give 1.71 g. of substantially pure Δ^{17}-3,11(β),21-trihydroxy-20-cyano-pregnene which was obtained in the form of colorless needles containing two molecules of benzene of crystallization; M. P. 99.5–105° C. (vigorous evolution of gas). The sample exhibited

$$\lambda_{max.}^{CH_3OH}\ 2230\ \text{Å.},\ E_{1\ cm.}^{1\%}\ 268$$

and the infrared absorption spectrum showed the complete absence of the carbonyl absorption band, as well as identity of this material with Δ^{17}-3,11(β),21-trihydroxy-20-cyano-pregnene prepared by the lithium borohydride reduction of Δ^{17}-3,21-dihydroxy-11-keto-20-cyano-pregnene as described in Example 5 hereinabove.

Example 9

2.32 grams of Δ^{17}-3,3-diethoxy-11-keto-20-cyano-21-hydroxy-pregnene was dissolved in 20 ml. of tetrahydrofuran, and to this solution was added a solution of 0.84 g. of sodium borohydride in 10 ml. of tetrahydrofuran, 10 ml. of water and 0.2 ml. of 2.5 N aqueous sodium hydroxide. The mixture was heated under reflux for a period of approximately 20 hours. The reaction mixture was then cooled to room temperature, and 35 ml. of 10% aqueous acetic acid was added to the cooled mixture thereby decomposing excess sodium borohydride.

The resulting clear, colorless solution was evaporated in vacuo to a volume of about 40–50 ml., and the pale-yellow oil which separated was extracted with three 50 ml. portions of ethyl acetate. The ethyl acetate extracts were combined and the resulting ethyl acetate solution was washed successively with two 50 ml. portions of water, with two 50 ml. portions of 5% aqueous sodium bicarbonate solution, with one 50 ml. portion of water, and with one 50 ml. portion of saturated aqueous sodium chloride solution. The washed ethyl acetate solution was dried over 5 g. of anhydrous magnesium sulfate, the solution was filtered, and the solvent was evaporated therefrom in vacuo to give 1.985 g. of Δ^{17}-3,3-diethoxy-11(β),21-dihydroxy-20-cyano-pregnene which was obtained in the form of a pale buff-colored amorphous solid.

This material was dissolved in 25 ml. of acetone, and to this solution was added 5 ml. of water and 0.2 ml. of 2.5 N aqueous hydrochloric acid. This solution was allowed to stand at room temperature for a period of approximately 20 hours, 5.0 ml. of 5% aqueous sodium bicarbonate solution and 20 ml. of water were added thereto, and the resulting solution was evaporated in vacuo to a small volume, thereby removing the major portion of the acetone. The buff-colored oil which separated was extracted with one 50 ml. portion and two 30 ml. portions of ethyl acetate. The ethyl acetate extracts were combined and the ethyl acetate solution was washed successively with two 40 ml. portions of water, with one 40 ml. portion of 5% aqueous sodium bicarbonate solution, with one 40 ml. portion of water, and with one 40 ml. portion of saturated aqueous sodium chloride solution. The washed ethyl acetate solution was dried over 5 g. of anhydrous magnesium sulfate, the solution was filtered, and the ethyl acetate was evaporated therefrom in vacuo to give a partly crystalline pale, buff-colored residue weighing 1.705 g. This material was recrystallized from acetone to give 0.73 g. of substantially pure Δ^{17}-3-keto-11(β),21-dihydroxy-20-cyano-pregnene which was obtained in the form of rosettes of heavy colorless needles; M. P. 215–218° C. with softening at 213° C. (partly melted at 203–206° C., then resolidified); no depression in melting point was observed when this material was mixed with Δ^{17}-3-keto-11(β),21-dihydroxy-20-cyano-pregnene prepared as described in Example 1.

Various changes and modifications may be made in carrying out the present invention without departing from the spirit and scope thereof. Insofar as these changes and modifications are within the purview of the annexed claims, they are to be considered as part of the present invention.

We claim:

1. The process of reducing a ketone grouping in a keto-substituted steroid compound containing at least one unsaturated carbon to nitrogen linkage, without substantially affecting said carbon to nitrogen linkage, which comprises reacting said keto-substituted steroid compound with an alkali metal borohydride thereby forming the corresponding hydroxy-substituted steroid compound.

2. The process of reducing a ketone grouping in a keto-substituted steroid compound containing at least one unsaturated carbon to nitrogen linkage, without substantially affecting said carbon to nitrogen linkage, which comprises reacting said keto-substituted steroid compound with lithium borohydride thereby forming the corresponding hydroxy-substituted steroid compound.

3. The process of reducing a ketone grouping in a keto-substituted steroid compound containing at least one unsaturated carbon to nitrogen linkage, without substantially affecting said carbon to nitrogen linkage, which comprises reacting said keto-substituted steroid compound with sodium borohydride thereby forming the corresponding hydroxy-substituted steroid compound.

4. The process of reducing the 11-keto-substituent in an 11-keto-10,13-dimethyl-cyclopentanopolyhydrophenanthrene compound containing at least one unsaturated carbon to nitrogen linkage, without substantially affecting said carbon to nitrogen linkage, which comprises bringing said 11-keto-10,13-dimethyl-cyclopentanopolyhydrophenanthrene compound into intimate contact with an alkali metal borohydride thereby forming the corresponding 11-hydroxy-10,13 - dimethyl - cyclopentanopolyhydrophenanthrene compound.

5. The process of reducing the 11-keto substituent in an 11-keto-10,13-dimethyl-cyclopentanopolyhydrophenanthrene compound containing at least one unsaturated carbon to nitrogen linkage, without substantially affecting said carbon to nitrogen linkage, which comprises bringing said 11-keto-10,13-dimethyl-cyclopentanopolyhydrophenanthrene compound into intimate contact with lithium borohydride thereby forming the corresponding 11-hydroxy-10,13-dimethyl - cyclopentanopolyhydrophenanthrene compound.

6. The process of reducing the 11-keto substituent in an 11-keto-10,13-dimethyl-cyclopentanopolyhydrophenanthrene compound containing at least one unsaturated carbon to nitrogen linkage, without substantially affecting said carbon to nitrogen linkage, which comprises bringing said 11 - keto - 10,13 - dimethyl - cyclopentanopolyhydrophenanthrene compound into intimate contact with sodium borohydride thereby forming the corresponding 11-hydroxy-10,13-dimethyl - cyclopentanopolyhydrophenanthrene compound.

7. The process of converting an 11-keto-10,13-dimethyl - cyclopentanopolyhydrophenanthrene compound containing at least one unsaturated carbon-nitrogen linkage to the corresponding 11(β) - hydroxy - 10,13 - dimethyl - cyclopentanopolyhydrophenanthrene compound without substantially affecting the carbon-nitrogen linkage, which comprises reacting said 11-keto-10,13-dimethyl - cyclopentanopolyhydrophenanthrene compound with an alkali metal borohydride, said reaction being carried out by bringing the reactants together in solution in an organic solvent at a temperature within the range of 0 to 70° C.

8. The process which comprises reacting an alkali metal borohydride with an 11-keto-pregnene compound having attached to the carbon atom in the 20-position of the molecule a substituent containing an unsaturated carbon to nitrogen linkage, thereby converting the 11-keto substituent to an 11(β)-hydroxy radical without substantially affecting the carbon to nitrogen linkage in the substituent attached to the 20-carbon atom.

9. The process of preparing Δ^{17}-3-semicarbazido-11(β),21 - dihydroxy - 20 - cyano - pregnene which comprises reacting Δ^{17}-3-semicarbazido-11 - keto - 20 - cyano - 21 - hydroxy - pregnene with lithium borohydride, said reaction being carried out by bringing the reactants together in solution in tetrahydrofuran at a temperature of approximately 25° C.

10. The process of preparing Δ^{17}-3,3-diethoxy-11(β),21 - dihydroxy - 20 - cyano - pregnene which comprises reacting Δ^{17}-3,3-diethoxy-11-keto-20-cyano-21-hydroxy-pregnene with lithium borohydride, said reaction being carried out by bringing the reactants together in solution in tetrahydrofuran at a temperature of approximately 25° C.

11. The process of preparing Δ^{17}-3,11(β),21-trihydroxy-20-cyano-pregnene which comprises reacting Δ^{17} - 3,21-dihydroxy - 11 - keto - 20-cyano-pregnene with lithium borohydride, said reaction being carried out by bringing the reactants together in solution in tetrahydrofuran at a temperature of approximately 25° C.

12. The process of preparing Δ^{4}-3,20-disemicarbazido - 11(β),17,21 - trihydroxy - pregnene, which comprises reacting Δ^{4}-3,20-disemicarbazido-11-keto-17,21-dihydroxy-pregnene with sodium borohydride, said reaction being carried out by bringing the reactants together in solution in tetrahydrofuran at a temperature of approximately 60–70° C.

13. The process of preparing Δ^{17}-3,11(β),21-trihydroxy-20-cyano-pregnene which comprises reacting Δ^{17}-3,11-diketo-20-cyano-21-hydroxy-pregnene with sodium borohydride, said reaction being carried out by heating a solution of the reactants in tetrahydrofuran under reflux.

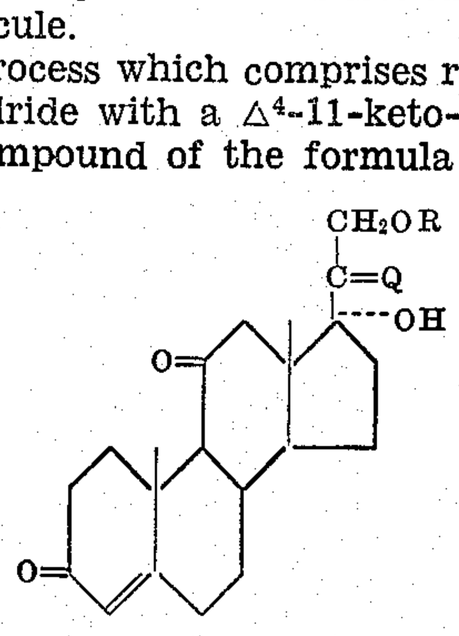
14. The process of converting a Δ^{17}-11-keto-20-cyano-pregnene compound to the corresponding Δ^{17}-11(β)-hydroxy-20-cyano-pregnene compound without substantially affecting the carbon to nitrogen linkages in the 20-cyano radical, which comprises reacting said Δ^{17}-11-keto-20-cyano-pregnene compound with an alkali metal borohydride.

15. The process of converting a Δ^{17}-11-keto-20-cyano-pregnene compound to the corresponding Δ^{17}-11(β)-hydroxy-20-cyano-pregnene compound without substantially affecting the carbon to nitrogen linkages in the 20-cyano radical, which comprises reacting said Δ^{17}-11-keto-20-cyano-pregnene compound with lithium borohydride.

16. The process of converting a Δ^{17}-11-keto-20-cyano-pregnene compound to the corresponding Δ^{17}-11(β)-hydroxy-20-cyano-pregnene compound without substantially affecting the carbon to nitrogen linkages in the 20-cyano radical, which comprises reacting said Δ^{17}-11-keto-20-cyano-pregnene compound with sodium borohydride.

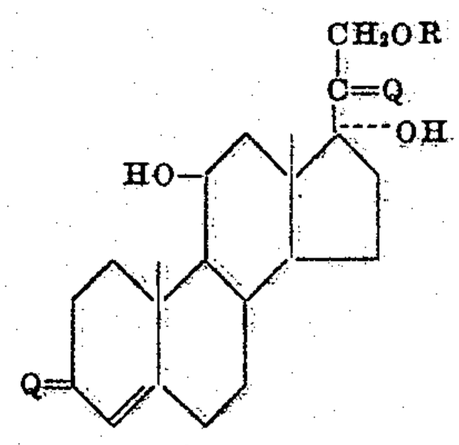
17. The process which comprises reacting an alkali metal borohydride with a Δ^{4}-11-keto-17-hydroxy-pregnene compound having substituted imino groupings attached to the 3- and 20-carbon atoms, and having a 21-position substituent selected from the group which consists of hydroxy and acyloxy radicals, thereby converting the 11-keto radical to an 11(β)-hydroxy grouping without affecting the other substituents present in the molecule.

18. The process which comprises reacting lithium borohydride with a Δ^{4}-11-keto-17-hydroxy-pregnene compound of the formula:



wherein R is a radical selected from the class which consists of hydrogen and acyl radicals, and Q is a radical selected from the class which consists of oximino, semicarbazido and aryl-hydra-

zino radicals, to produce a compound of the formula:



wherein R and Q have the significance above defined.

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