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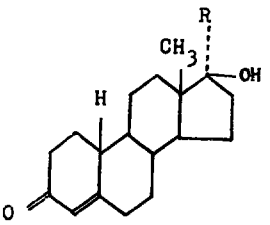
COMPLETE SPECIFICATION

17-Alkyl-19-Nortestosterones and their Preparation

We, G. D. SEARLE & Co. of Skokie, State of Illinois, United States of America, a corporation formed under the laws of the State of Illinois, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a new group of hypotensive and anabolic agents with low androgenic activity and, more particularly, to 19-nortestosterone derivatives substituted in the 17-position by a lower alkyl radical containing 2—8 carbon atoms.

These compounds can be represented by the general structural formula



wherein R is a lower alkyl radical containing 2—8 carbon atoms such as ethyl, straight and branched propyl, butyl, pentyl, hexyl, heptyl, and octyl.

The compounds of the present invention are valuable anabolic agents, i.e. they promote nitrogen retention. They produce this effect at a dosage which causes only a very low degree of androgenic activity. It is well known that testosterone propionate is an effective anabolic agent but its clinical utility for that purpose is greatly limited because in many patients the androgenic effects are undesirable. In the case of the claimed compounds the effective anabolic doses are so small that prolonged administration becomes practical without undesirable side effects.

Another important field of utility of these compounds is their anti-hypertensive effect an effect which is not shared by 19-nortestosterone or its 17-methyl derivative. The compounds of this invention are particularly effective in overcoming the hypertension produced by the ~~mineral corticoid~~ hormone desoxycorticosterone.

Intermediates useful in the manufacture of these 17-alkyl substitution products of 19-nortestosterone are described in U.S.A. Specifications Nos. 2,655,518, 2,666,769, 2,691,028, 2,702,811 and 2,704,768.

In accordance with the invention the preferred process for the manufacture of these compounds is the isomerization of a 3-oxo-17α-alkyl-5(10)-estren-17-ol under the influence of a basic isomerization agent such as sodium hydroxide in aqueous methanol, or an acidic isomerization agent, such as hydrochloric acid or *p*-toluenesulphonic acid in aqueous methanol, whereby the double bond migrates from the 5—10 position into the 4—5 position to give a compound of the desired composition. A 3-oxo-17α-alkyl-5(10)-estren-17-ol is conveniently prepared by the reaction sequence which comprises the ethynylation with acetylene of a lower alkyl ether of estrone, catalytic hydrogenation of the 17α-ethynyl group to a 17α-ethyl group, and a Birch type of reduction of the resulting 17α-alkylestradiol 3-~~monoalkyl~~ ether with lithium and ammonia, followed by a mild acidic hydrolysis. It should be understood that this is a particular illustration of a general process. In a useful modification of this process, the product of the Birch reduction, a 17α-alkyl-3-alkoxy-2,5(10)-estradien-17-ol, is subjected to a more vigorous acidic hydrolysis whereby cleavage of the enol ether function at position 3, ketonization of the resulting 3-enol and rearrangement of the 5—10 double bond into conjugation with the 3-ketone take place as a single operation in a single reaction vessel without the necessity of isolating the 3-oxo-17α-alkyl-5(10)-estren-17-ol which is formed as an intermediate product. It will be apparent that the direct conversion of a 17α-alkyl-

[*Price 3s. 6d.*]

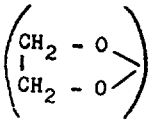
3-alkoxy-2,5(10)-estradien-17-ol to a 17-alkyl-19-nortestosterone is equivalent to the isomerization of a 3-oxo-17α-alkyl-5(10)-estren-17-ol to a 17-alkyl-19-nortestosterone, and that these are alternative modifications of a single process, involving an optional selection of operating details. In the direct conversion of the homoannular unconjugated diene, 17α-alkyl-3-alkoxy-2,5(10)-estradien-17-ol, 3-oxo-17α-alkyl-5(10)-estren-17-ol appears in the reaction mixture as an unisolated intermediate which is isomerized to the 17-alkyl-19-nortestosterone.

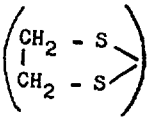
A second process for the manufacture of a 17-alkyl-19-nortestosterone is the hydrogenation of a 17α-substitution product of 19-nortestosterone in which the 17α-substituent is an unsaturated aliphatic hydrocarbon radical. Some of these substitution products form the subject matter of our Application No. 24589/56 (Serial No. 789,066). Such radicals can incorporate unsaturated linkages of either the ethylene or acetylene type and include, illustratively, ethynyl, propynyl, butynyl, pentynyl, hexynyl, heptynyl and octynyl as well as vinyl, propenyl, allyl, and higher homologs thereof.

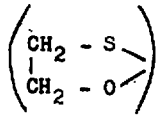
As an example of a method for carrying out such a hydrogenation, 17α-ethynyl-19-nortestosterone, in a solution or suspension, is shaken in a hydrogen atmosphere in the presence of a suitable catalyst, for example a noble metal catalyst such as palladium on charcoal This compound is reduced in stages to 17α-vinyl-19-nortestosterone and then to 17-ethyl-19-nortestosterone. Under the reaction conditions described herein, hydrogenation of the nuclear double bond is a relatively minor side reaction. A useful, and obviously equivalent modification of this procedure for the manufacture of 17-ethyl-19-nortestosterone is the catalytic reduction of 17α-vinyl-19-nortestosterone. The 17α-substitution products of 19-nortestosterone in which the 17α-substituent is an unsaturated aliphatic hydrocarbon radical are conveniently prepared by a variety of procedures which involve the addition of acetylene, a homologue of acetylene, or an organo-metallic compound to a steroidal 17-ketone. For example, 17α-ethynyl-19-nortestosterone can be prepared by the addition of acetylene to 3-methoxy-2,5(10)-estradien-17-one, followed by acid catalyzed hydrolysis and isomerization of the resulting product. The addition of allylmagnesium bromide to 3-methoxy-2,5(10)-estradien-17-one followed by acidic hydrolysis and isomerization affords 17-allyl-19-nortestosterone.

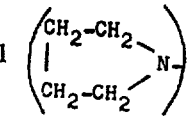
A third process for the manufacture of a 17-alkyl-19-nortestosterone comprises the treatment with acid in the presence of a hydroxylic medium of a nuclearly unsaturated derivative of a 17α-alkyl-19-norandrostan-17β-ol which is further substituted at position 3 by at least one hetero atom to which is attached a hydrocarbon residue, said nuclear unsaturation being exclusive of a homoannular unconjugated diene, and in which said nuclear unsaturation and the group substituted at position 3 jointly result in an atomic arrangement which is convertible to a Δ^4-3-ketone by acidic hydrolysis.

The word "hetero" as used in the expression "hetero atom" is defined herein to include elements of Groups 5 and 6 of the Periodic Table of Elements, such as oxygen, sulphur and nitrogen. A group substituted at position 3 can therefore be, illustratively, an ethoxyl or other alkoxyl group, an ethylthio or other alkylthio group, benzylthio,

ethylenedioxy 

ethylenedithio 

ethylenethiooxy 

and N-pyrrolidyl 

The nuclear unsaturation is restricted to rings A and B of the steroid molecule, and can consist of a single double bond having a terminus at position 5, or a conjugated system of two double bonds, one of which has a terminus at position 5. The hydrolysis of a homoannular unconjugated diene, such as a 17α-alkyl-3-alkoxy-2,5(10)-estradien-17-ol, is outside the scope of this process, as such an operation proceeds through and is the equivalent of the isomerization of a 3-oxo-17α-alkyl-5(10)-estren-17-ol. Compounds comprehended as starting materials for the hydrolytic operations of this process consequently include compounds having a single nuclear double bond with a terminus at position 5, such as 3-ketals, 3-mercaptoles, and 3-hemithioketals, as well as compounds having 2 conjugated double bonds of which one has a terminus at position 5, such as enol ethers, enol thioethers, and 3-N-pyrrolidyl dienes. However, because of the relatively good yields involved in their preparation and hydrolysis, and because of the relative freedom from unwanted side reactions, use of enol alkyl ethers and ethylene ketals is preferred in the hydro-

lytic operations of this process. The enol ethers, enol thioethers, ketals, mercaptoles, hemithioketals and tertiary amine derivatives comprehended for use in this process can be prepared, as described hereinafter, by the introduction of the appropriate group at position 3 of 19-nortestosterone or 19-norandrostenedione, followed by introduction of the 17α-alkyl substituent by reaction with an organo-metallic reagent, such as an alkylmagnesium halide or an alkyllithium. A typical product of such as reaction sequence is 17α-ethyl-3-ethoxy-19-nor-3,5-androstadien - 17-ol, formed as described hereinafter by the addition of ethylmagnesium bromide to 3-ethoxy-19-nor-3,5 - androstadien - 17 - one. Hydrolysis of the protecting group at position 3 is then achieved by treatment with an acid in the presence of a hydroxylic medium. This hydroxylic medium can include water, as well as such materials as alcohols and carboxylic acids, and can even include such materials as ketones which are in equilibrium with a tautomer containing a hydroxyl group. Acids employed can be either mineral or organic acids or mixtures thereof. In general, the rate of hydrolysis increases with the strength of the acid and the reaction temperature, and it is convenient to choose acidic reagents and reaction temperatures which will complete the hydrolysis reaction in a reasonably short period of time, while causing only a minimum amount of dehydration of the 17-hydroxyl group. The hydrolysis of compounds such as 3-mercaptoles and 3 - hemithioketals by mixtures which generate acid during the course of the reaction, such as a mixture of acetone, cadmium carbonate and mercuric chloride, is also included within the scope of this process.

The compounds and methods of manufacture which constitute this invention will appear more fully from the following examples. In these examples quantities are given in parts by weight and temperatures in degrees Centigrade (° C.).

EXAMPLE 1.

To a refluxing solution of 47.5 parts of 3-methoxy-13-methyl-17α-ethynyl-1,4,6,7,8,9,11,12,13,14,16,17 - dodecahydro - 15H - cyclopenta[a]phenanthren-17-ol in 3200 parts of methanol and 1000 parts of water are added 240 parts of concentrated hydrochloric acid. Refluxing is continued for an additional 5 minutes after which the solution is maintained at room temperature for 15 minutes. Then 13,000 parts of water are added and the mixture is cooled to 0° C. After standing for several hours at that temperature, the mixture is filtered and the precipitate is dried and crystallized from ethyl acetate. The 17-ethynyl-19-nortestosterone thus obtained melts at about 202—204° C.

Through a mixture of 11 parts of charcoal containing 5% palladium and 2000 parts of dioxane a stream of hydrogen is passed for 60 minutes. Then 86 parts of 17-ethynyl-19-nortestosterone in 1500 parts of dioxane are added and the mixture is hydrogenated until 2 moles of ~~hydrogen~~ are absorbed. The catalyst is then removed by filtration and the solvent is evaporated under vacuum. The crystalline residue is dissolved in 2700 parts of benzene and thus applied to a chromatography column containing 5000 parts of silica gel. The column is washed with 2700 parts of benzene, 4500 parts of a 10% solution of ethyl acetate in benzene and 27,000 parts of a 20% solution of ethyl acetate in benzene and is then eluted with 30,000 parts of a 30% solution of ethyl acetate in benzene. The resulting eluate is concentrated under vacuum and the residue is recrystallized from methanol and dried to constant weight at 75° C. The 17-ethyl-19-nortestosterone thus obtained melts at about 140—141° C. Its ultraviolet absorption spectrum shows a maximum at 240 millimicrons with a molecular extinction coefficient of 16,500.

EXAMPLE 2.

To a stirred mixture of 8.5 parts of magnesium in 140 parts of ether there are added 5 parts of allyl bromide in 15 parts of ether. Then, in the course of 45 minutes, a mixture of 20 parts of the methyl ether of estrone and 95 parts of allyl bromide in 630 parts of ether are added. After 3 hours of refluxing the mixture is cooled to 0° C., washed repeatedly with 10% ammonium chloride solution and then with water, dried over anhydrous sodium sulphate, filtered and evaporated. The residue is taken up in ether. The ether solution is partially concentrated and diluted with petroleum ether. The crystalline 17α-allyl-3-methoxy-1,3,5(10)-estratrien-17-ol thus obtained melts at about 91—91.5° C.

A mixture of 11.5 parts of 17α-allyl-3-methoxy-1,3,5(10)-estratrien-17-ol, 3 parts of charcoal containing 5% palladium and 160 parts of ethanol is hydrogenated until one mole of hydrogen has been absorbed. The mixture is then filtered through filter aid and the filtrate is evaporated under vacuum. The residue is crystallized from a mixture of ether and methanol to yield 17α-propyl-3 - methoxy-1,3,5(10)-estratrien-17-ol melting at about 93—94° C.

To a stirred mixture of 6 parts of 17α-propyl-3-methoxy-1,3,5(10)-estratrien-17-ol in 500 parts of liquid ammonia and 140 parts of ether, 7 parts of lithium are added in the course of 20 minutes. The mixture is stirred for 30 minutes after which 46 parts of ethanol are added dropwise in the course of an hour. Stirring is continued until all of the ammonia has disappeared. Then water is added and the ether layer is separated, washed with water, dried over anhydrous sodium sulphate, filtered and evaporated. Crystallization from a mix-

ture of ether in methanol yields 17α-propyl-3-methoxy-2,5(10)-estradien-17-ol melting at about 150—152° C.

A mixture of 18 parts of 17α-propyl-3-methoxy-2,5(10)-estradien-17-ol, 320 parts of methanol, 80 parts of water, and 18 parts of concentrated hydrochloric acid is refluxed for 5 minutes and then permitted to stand for 15 minutes in hot water. A sufficient amount of hot water is added until the mixture becomes turbid. Upon standing 17-propyl-19-nortestosterone precipitates which, crystallized from a mixture of acetone and petroleum ether, melts at 120—122° C.

EXAMPLE 3.

To a stirred suspension of 16.5 parts of the methyl ether of estrone in 300 parts of ether there is added a solution of butyl lithium prepared from 115 parts of 1-bromobutane and 6.7 parts of lithium in 600 parts of ether. Stirring is continued for an hour after which the mixture is decomposed with methanol and dilute sulphuric acid and extracted with ether. This extract is washed with saturated sodium chloride solution, dried over anhydrous sodium sulphate, filtered and evaporated under nitrogen. The residue is crystallized from methanol and water and then applied in benzene solution to a chromatography column containing 1000 parts of allumina. The column is washed with 1800 parts of a 10% solution of petroleum ether in benzene and then eluted with 9000 parts of a 10% solution of petroleum ether in benzene. This eluate is evaporated and the residue is recrystallized from aqueous methanol to yield 3 - methoxy-17α-butyl-1,3,5(10)-estratrien-17β-ol.

To a solution of 37.2 parts of this compound in 500 parts of ether and 500 parts of liquid ammonia are added 3.5 parts of short strips of lithium wire with stirring. The dark blue solution is stirred for 10 minutes after which 32 parts of methanol are added dropwise in the course of 15 minutes to decolorize the solution. Then 56 additional parts of methanol are slowly added and, after most of the ammonia has been evaporated, 1100 parts of ether and 700 parts of water are added with stirring. The organic layer is separated, washed with saturated sodium chloride solution, dried over sodium sulphate, filtered and concentrated under vacuum. To the oily residue are added 1110 parts of methanol and 500 parts of water and the mixture is heated to reflux. Then 240 parts of concentrated hydrochloric acid are added and refluxing is continued for 6 minutes. The mixture is then extracted with ether. The ether solution is washed with a saturated solution of sodium chloride, dried over sodium sulphate, filtered and evaporated under vacuum. The residue is applied in benzene to a chromatography column containing 350 parts of silica gel. The column is washed with 500 parts of benzene and then with 3000 parts of a 10% solution of ethyl acetate in benzene. Elution with 2000 parts of a 20% solution of ethyl acetate in benzene, concentration of the eluate and crystallization from aqueous methanol then yields 17-butyl-19-nortestosterone which melts at about 127—128° C.

EXAMPLE 4.

Substitution of an equivalent amount of 1-bromooctane for the 1-bromobutane in the process of the preceding example yields 17-octyl-19-nortestosterone. The infrared absorption spectrum of that compound shows maxima at 2.8 and 6.05 microns. The ultraviolet absorption spectrum shows a maximum at 240.5 millimicrons with a molecular extinction coefficient of 17,000.

EXAMPLE 5.

A mixture of 10 parts of 17α-ethynyl-3-methoxy-1,3,5(10)-estratrien-17-ol, 2.5 parts of 5% palladium on charcoal catalyst and 50 parts of dioxan is shaken in contact with a hydrogen atmosphere until 2 molecular equivalents of hydrogen have been consumed. The catalyst is removed by filtration, and the residue remaining after concentration of the filtrate is purified by recrystallization from a mixture of ether and petroleum ether. In this manner there is obtained 17α-ethyl-3 - methoxy-1,3,5(10)-estratrien-17-ol melting at about 88—89° C.

A solution of 50 parts of 17α-ethyl-3-methoxy-1,3,5(10)-estratrien-17-ol in 710 parts of ether is diluted with 2500 parts of liquid ammonia. Throughout the following operations, until the reaction mixture is diluted with water, it is constantly stirred and is maintained at an approximately constant volume by the addition of a total of 2100 parts of ether in portions, to replace the ammonia which is continuously lost by vaporization. The solution of 17α-ethyl-3-methoxy-1,3,5(10)-estratien-17-ol in ether and liquid ammonia is treated over a period of 35 minutes by the addition of a total of 35 parts of lithium in small portions. After an additional hour, 240 parts of ethanol is added in small portions over a period of 3 hours, and stirring is continued for several hours more. Water (1000 parts) is added, and the ethereal phase is washed with several portions of water, dried and concentrated. The residue obtained by evaporation of the ethereal solution is stirred with a mixture of 200 parts of methanol and 1 part of pyridine, and the resulting suspension is refrigerated for several hours. The crystalline product is collected on a filter and washed with 120 parts of cold-methanol. This compound is 17α-ethyl-3-methoxy-2,5(10)-estradien-17-ol melting at about 127—128° C.

A mixture of 1.25 parts of 17α-ethyl-3-methoxy-2,5(10)-estradien-17-ol, 24 parts of methanol and 4 parts of acetic acid is heated under reflux for 5 minutes. Water (150 parts)

is added and the mixture is refrigerated for several hours. The precipitated product is collected on a filter and dried. Recrystallization from a mixture of acetone and petroleum ether affords 17α-ethyl-3-oxo-5(10)-estren - 17 - ol melting at about 134—136° C.

A mixture of 10 parts of 17α-ethyl-3-oxo-5(10)-estren-17-ol, 160 parts of methanol, 20 parts of water and 7 parts of concentrated hydrochloric acid is stirred for 2 hours at room temperature and is then chilled and allowed to stand at 0° C. for 2 hours. The mixture is filtered from a small amount of insoluble material, and the filtrate is diluted, with constant stirring with 500 parts of water. The mixture is then cooled to about 0—5° C. and filtered. The crystalline product can be purified by recrystallization from aqueous methanol, or from a mixture of acetone and petroleum ether. In this manner there is obtained 17-ethyl-19-nortestosterone melting at about 140—141° C.

EXAMPLE 6.

A mixture of 36 parts of 17α-ethyl-3-methoxy-2,5(10)-estradien-17-ol, 475 parts of methanol, 70 parts of water and 25 parts of concentrated hydrochloric acid is stirred for 2 hours at room temperature and is then allowed to stand at 0—10° C. for about 2 hours. The mixture is filtered from a small amount of insoluble material, and the filtrate is diluted, with constant stirring, with 2000 parts of water. The mixture is then cooled to about 0—5° C., and the crystalline product is collected on a filter. Recrystallisation from aqueous methanol or from a mixture of acetone and petroleum ether yields purified 17-ethyl-19-nortestosterone melting at about 140—141° C.

In the same manner, 17α-ethyl-3-ethoxy-2,5(10)-estradien-17-ol (obtained by ethynylation of estrone ethyl ether followed by hydrogenation of the ethynyl group and reduction of the resulting product with lithium and ammonia) yields 17-ethyl-19-nortestosterone by treatment with mineral acid as described above.

EXAMPLE 7.

A mixture of 5 parts of 17-allyl-19-nortestosterone (prepared as described in our Specification No. 24589/56 (Serial No. 789,066)), 100 parts of dioxan and 1.5 parts of 5% palladium on charcoal catalyst is shaken in contact with a hydrogen atmosphere until approximately 1 molecular equivalent of hydrogen has been consumed. The catalyst is removed by filtration and the filtrate is concentrated under reduced pressure. When the *residue* obtained by vaporization of the solvent is recrystallized repeatedly from a mixture of acetone and petroleum ether, there is obtained 17-propyl-19-nortestosterone melting at about 120—122° C.

EXAMPLE 8.

A mixture of 53.7 parts of 17-ethynyl-19-nortestosterone, 1500 parts of dioxane, 1000 parts of pyridine and 30 parts of a 5% palladium on calcium carbonate catalyst is shaken in contact with a hydrogen atmosphere until approximately 1 molecular equivalent of hydrogen has been consumed. At this point the hydrogenation is stopped and the catalyst is removed by filtration. The filtrate is concentrated under vacuum to about 500 parts, diluted with 3000 parts of ether and washed with normal hydrochloric acid until a Congo Red test shows an acidic reaction. The solution is washed successively with water, with 5% sodium bicarbonate solution, again with water and with saturated sodium chloride solution. The ethereal phase is dried over sodium sulphate, concentrated on a steam bath to about 500 parts and diluted with 800 parts of petroleum ether. After storage at 0° C. for 16 hours the product is collected on a filter, dried and crystallized from a mixture of ethyl acetate and petroleum ether. In this manner there is obtained 17-vinyl-19-nortestosterone melting at about 169—171° C.

A mixture of 10 parts of 17-vinyl-19-nortestosterone, 80 parts of dioxane and 3 parts of a 5% palladium on charcoal catalyst is shaken in contact with a hydrogen atmosphere until approximately 1 molecular equivalent of hydrogen has been consumed. The catalyst is removed by filtration, and the filtrate is concentrated to dryness under reduced pressure. Recrystallization of the residue from methanol affords 17-ethyl-19-nortestosterone melting at about 140—141° C.

EXAMPLE 9.

Potassium (7.8 parts), washed with toluene, tertiary amyl alcohol and ether, is added to 125 parts of tertiary amyl alcohol, and the stirred reaction mixture is heated under reflux in a nitrogen atmosphere for 2 hours. It is then cooled to about 0° C., and a solution of 24 parts of 1-octyne in 90 parts of ether is added. After the mixture is stirred for an additional hour, a suspension of 5.7 parts of estrone methyl ether in ether is added rapidly. The reaction mixture is stirred in a nitrogen atmosphere at about 0° C. for 5 more hours, after which it is allowed to warm to room temperature and is stirred for an additional 16 hours. It is again cooled to 0° C., and mixed well with a solution of 15 parts of ammonium chloride in 150 parts of water. The ethereal phase is separated, washed with several portions of ammonium chloride solution and with water, dried, and concentrated to a residual brown oil. A mixture of 4 parts of this crude product (which is predominantly 17α-octynyl-3-methoxy-1,3,5(10)-estratrien-17-ol), 1 part of 5% palladium on charcoal catalyst and 75 parts of dioxane is shaken in contact with a hydrogen atmosphere until the absorption of hydrogen, which is initially quite rapid, has become very slow. Up to approximately 2 molecular equivalents of hydrogen will have

been consumed at this point. The catalyst is removed by filtration, and the residue remaining after concentration of the filtrate is purified by chromatographic fractionation on a silica gel column or by recrystallization from methanol. In this manner there is obtained 17α-octyl-3-methoxy-1,3,5(10)-estratrien - 17-ol melting at about 80—81° C.

A solution of 2.5 parts of 17α-octyl-3-methoxy - 1,3,5(10) - estratrien-17 - ol in 70 parts of ether is diluted with 205 parts of liquid ammonia. This stirred solution is treated over a period of 30 minutes by the addition of a total of 2.5 parts of lithium in small portions. After an additional hour, 20 parts of ethanol is added in small portions over a period of 3 hours, and stirring is continued for several hours more. Throughout the preceding operations, an additional 70 parts of ether is gradually added to replace some of the ammonia which is lost by vaporization. Water (80 parts) is added, and the ethereal phase is washed with several portions of water, dried and concentrated. The residue obtained by evaporation of the ethereal solution is washed with a small volume of cold methanol containing about 1% of pyridine, and it is then purified by recrystallization from a mixture of ether and methanol. In this manner there is obtained 17α-octyl-3 - methoxy - 2,5(10)-estradien-17-ol melting at about 50—~~50~~° C. A mixture of 1.1 parts of this compound, 24 parts of methanol, 6 parts of water and 1.2 parts of concentrated hydrochloric acid is heated under reflux for 10 minutes, cooled, and diluted with several times its volume of water. Purification of the precipitated product by crystallization from aqueous methanol affords 17-octyl-19-nortestosterone melting at about 120—122° C.

EXAMPLE 10.

19-Nor-4-androstene-3,17-dione (Journal of the American Chemical Society, *75*, 5366 (1953)) is converted to 3-ethoxy-19-nor-3,5-androstadien-17-one (Journal of the American Chemical Society, *76*, 4093 (1954)). A stirred solution of 6 parts of this enol ether in 70 parts of anhydrous ether is treated by the gradual addition of an ethereal solution of 50 parts of ethyl-magnesium bromide. The reaction mixture is maintained under reflux for 2 hours by application of external heat as necessary, and it is then poured into ice water and made distinctly acidic by the addition of hyrochloric acid. Sufficient methanol is added to produce a single phase solution, and this acidified solution is stirred at room temperature for 4 hours, after which it is concentrated under reduced pressure until most of the methanol and ether are removed. The aqueous suspension which remains is extracted repeatedly with ether, and the combined ethereal extracts are washed with several portions of water, dried, and concentrated under reduced pressure. When the residue obtained by vaporization of the ether is recrystallized from a mixture of acetone and petroleum ether, there is obtained 17-ethyl-19-nortestosterone melting at about 140—141° C.

By the substitution of 60 parts of propylmagnesium bromide for the ethylmagnesium bromide in this procedure, there is obtained 17-propyl - 19 - nortestosterone melting at about 120—122° C.

EXAMPLE 11.

As far as possible, all of the following operations up to the isolation of the final product are carried out in a nitrogen atmosphere to minimize decomposition of the sensitive intermediates. A mixture of 10 parts of 19-nor-4-androstene-3,17 - dione, 880 parts of of benzene and 10 parts of pyrrolidine is heated at the boiling point for 1 hour in a reaction vessel equipped with a water trap which continuously removes water from the condensed vapours and prevents it from returning to the reaction vessel. There is then added about 0.1 part of *p*-toluenesulphonic acid monohydrate and the mixture is maintained under reflux until no more water collects in the water trap. The reaction mixture is then washed with 3 small portions of water containing a trace amount of pyridine, and the organic phase is separated and concentrated to about 5% of its original volume under reduced pressure. The residue, which contains a 3-(N - pyrrolidyl)-19-norandrostadiene-17-one, is dissolved in anhydrous ether. An ethereal solution of 75 parts of ethylmagnesium bromide is added, and the reaction mixture is heated under reflux for 2 hours. The mixture is then poured into ice water and made distinctly acidic by the addition of hydrochloric acid. It is stirred at room temperature for 16 hours, after which the ethereal phase is separated and combined with ether extracts of the remaining aqueous liquor. The combined ethereal extracts are washed with 3 small portions of water and concentrated to dryness under reduced pressure. Purification of the residue by recrystallization from a mixture of acetone and petroleum ether affords 17-ethyl-19-nortestosterone melting at about 140—141° C.

EXAMPLE 12.

Ten parts of 19-nortestosterone is converted into ethylene ketal by heating it with 270 parts of benzene, 2.5 parts of ethylene glycol and 0.1 part of *p*-toluenesulphonic acid monohydrate in a reaction vessel equipped with a water trap which continuously removes water from the condensed vapours and prevents it from returning to the reaction vessel. The mixture is maintained under reflux for 24 hours, after which the benzene is removed by distillation under reduced pressure and the residue is recrystallized from methanol containing about 1% of pyridine. Five parts of this purified ethylene ketal is dissolved by warming it with 150 parts of pyridine. after

which the solution is cooled to room temperature and gradually added to an oxidizing reagent prepared by the cautious addition in small portions of 7 parts of chromium trioxide to 70 parts of pyridine. The reaction mixture is shaken well and allowed to stand at room temperature for 4 hours. The reaction mixture is then diluted with about 10 times its volume of water and extracted repeatedly with portions of a 50 volume per cent. solution of benzene in ether. The material which is insoluble in either phase is removed by filtration and discarded, and the combined organic extract is washed with 3 small portions of water and concentrated to dryness under reduced pressure. Purification of the residue by recrystallization from methanol containing a small amount of pyridine affords a norandrostenedione 3-ethylene monoketal. A solution of 3 parts of this compound and 32 parts of ethylmagnesium bromide in anhydrous ether is heated under reflux for 3 hours, after which it is poured into ice water and made distinctly acidic by the addition of hydrochloric acid. The acidified mixture is stirred for 2 hours at room temperature, and then the ethereal phase is separated and combined with ether extracts of the remainder of the mixture. To insure complete hydrolysis of the ethylene ketal, the residue remaining after distillation of the ether extract is redissolved in 80% acetic acid, and the solution is heated at 90—100° C. for one hour and concentrated to a small volume under reduced pressure. The residue is diluted with water and extracted with several portions of ether. The combined ether extract is washed with dilute sodium bicarbonate solution and with several portions of water and concentrated to dryness under reduced pressure. Purification of the residue by recrystallization from a mixture of acetone and petroleum ether affords 17-ethyl-19-nortestosterone melting at about 140—141° C.

EXAMPLE 13.

19-Nor-4-androstene-3,17-dione (8 parts) is converted into a 3-ethylene ketal by heating it under partial reflux for 5 hours with 150 parts of purified 2-methyl-2-ethyl-1,3-dioxolane (the ethylene ketal of butanone) which has been freed of ethylene glycol by efficient fractionation. and 0.2 part of *p*-toluene-sulphonic acid monohydrate. During the period of partial reflux, a distillate fraction of approximately 100 parts is collected and discarded. The reaction mixture is then cooled and diluted with benzene, after which it is washed with dilute sodium bicarbonate solution and with several portions of water. The organic phase is separated and concentrated to dryness under reduced pressure. Purification of the residue by crystallization from methanol containing a trace amount of pyridine affords a norandrostenedione 3-ethylene monoketal. A solution of 3 parts of this compound and 32 parts of ethylmagnesium bromide in anhydrous ether is heated under reflux for 3 hours, after which it is poured into ice water and made distinctly acidic by the addition of hydrochloric acid. The acidified mixture is stirred for 2 hours at room temperature, an then the ethereal phase is separated and combined with ether extracts of the remainder of the mixture. To insure complete hydrolysis of the ethylene ketal, the residue remaining after distillation of the ether extract is redissolved in 80% acetic acid, and the solution is heated at 90—100° C. for one hour and concentrated to a small volume under reduced pressure. The residue is diluted with water and extracted with several portions of ether. The combined ether extract is washed with dilute sodium bicarbonate solution and with several portions of water and concentrated to dryness under reduced pressure. Purification of the residue by recrystallization from a mixture of acetone and petroleum ether affords 17-ethyl-19-nortestosterone melting at about 140—141° C.

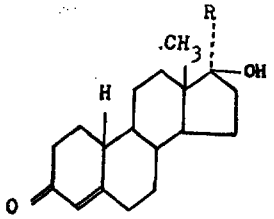
EXAMPLE 14.

A solution of 5 parts of 19-nortestosterone in 88 parts of benzene is heated under reflux for 8 hours with 10 parts of β-mercaptoethanol and 1 part of *p*-toluenesulphonic acid monohydrate. The reaction mixture is then cooled and washed with dilute sodium carbonate solution and with several portions of water. The organic phase is separated and concentrated to dryness under reduced pressure. Purification of the residue by repeated crystallization from methanol containing a trace amount of pyridine affords 19-nortestosterone 3-ethylene hemithioketal. Two parts of this ethylene hemithioketal is dissolved in 70 parts of warm pyridine. The solution is cooled to room temperature and gradually added to an oxidizing reagent prepared by the cautious addition in small portions of 2 parts of chromium trioxide to 20 parts of pyridine. The reaction mixture is shaken well and allowed to stand at room temperature for 4 hours. The reaction mixture is then diluted with about 10 times its volume of water and extracted repeatedly with portions of a 50 volume per cent. solution of benzene in ether. The material which is insoluble in either phase is removed by filtration and discarded, and the combined organic extract is washed with 3 small portions of water and concentrated to dryness under reduced pressure. Purification of the residue by recrystallization from methanol containing a small amount of pyridine affords a norandrostenedione 3-ethylene monohemithioketal. A solution of 1 part of this compound and 10 parts of ethylmagnesium bromide in anhydrous ether is heated under reflux for 3 hours, after which it is poured into ice water and made distinctly acidic by the addition of hydrochloric acid. The acidified mixture is stirred for 2 hours at

room temperature, and then the ethereal phase is separated and combined with ether extracts of the remainder of the mixture. The residue remaining after distillation of the ether extract is redissolved in a mixture of 125 parts of ethanol and 15 parts of water, and 3 parts of concentrated hydrochloric acid is added. The mixture is heated under reflux for 10 minutes and stirred at room temperature for an additional 6 hours. It is then neutralized with sodium bicarbonate and concentrated to a small volume under reduced pressure. The residue is diluted with water and extracted with several portions of ether. The combined ether extract is washed with several portions of water and is concentrated to dryness under reduced pressure. Purification of the residue by recrystallization from a mixture of acetone and petroleum ether affords 17-ethyl-19-nortestosterone melting at about 140—141° C.

What we claim is:—

1. Compounds of the general structural formula:



wherein R is a lower alkyl radical containing 2—8 carbon atoms.

2. 17-Ethyl-19-nortestosterone.

3. 17-*n*-Propyl-19-nortestosterone.

4. 17-*n*-Butyl-19-nortestosterone.

5. An isomerization process for preparing a 17α-alkyl-19-nortestosterone, wherein said alkyl group contains 2 to 8 carbon atoms, which comprises the treatment of a 3-oxo-17α-alkyl-5(10)-estren-17-ol with an acidic isomerization agent or a basic isomerization agent.

6. An isomerization process for preparing 17α-ethyl-19-nortestosterone which comprises treatment of 3-oxo-17α-ethyl-5(10)-estren-17-ol with an acidic isomerization agent.

7. An isomerization process for preparing 17α-ethyl-19-nortestosterone which comprises treatment of 3-oxo-17α-ethyl-5(10)-estren-17-ol with a mineral acidic isomerization agent.

8. A process as claimed in Claim 5 wherein the 3-oxo-17α-alkyl-5(10)-estren-17-ol is present as an unisolated intermediate in the conversion of a 17α-alkyl-3-alkoxy-2,5(10)-estradien-17-ol to a 17-alkyl-19-nortestosterone.

9. A process as claimed in Claim 6 or 7 wherein the 3-oxo-17α-ethyl-5(10)-estren-17-ol is present as an unisolated intermediate in the conversion of a 17α-ethyl-3-alkoxy-2,5(10)-estradien-17-ol to 17-ethyl-19-nortestosterone.

10. An isomerization process for preparing 17α-*n*-propyl-19-nortestosterone which comprises treatment of 3-oxo-17α-*n*-propyl-5(10)-estren-17-ol with an acidic isomerization agent.

11. An isomerization process for preparing 17α-*n*-propyl-19-nortestosterone which comprises treatment of 3-oxo-17α-*n*-propyl-5(10)-estren-17-ol with a mineral acidic isomerization agent.

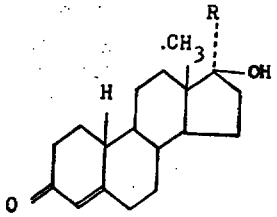
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* C L M S *