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COMPLETE SPECIFICATION

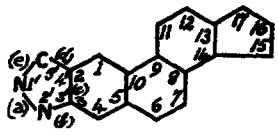
Steroid Compounds and preparation thereof

We, STERLING DRUG INC., a corporation organised under the laws of the State of Delaware, United States of America, of 1450, Broadway, New York, State of New York, 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:—

This invention relates to heterocyclic substituted steroids, and in particular it is concerned with steroido [3.2-c] pyrazoles and the preparation thereof, and to intermediates in the preparation thereof.

It has been found that new and useful compounds are produced when a pyrazole ring is fused through its 3- and 4-positions to the 3- and 2-positions, respectively, of a steroid nucleus, said steroid having from eighteen to twenty-three carbon atoms exclusive of ester radicals.

The ring structure of the compounds of the invention is represented by the following structure:



The exact nature of the steroid moiety is not critical. The utility of steroids, including those exhibiting hormonal or other pharmacological or endocrinological properties, is well known. Such steroid moieties have from eighteen to twenty-three carbon atoms, not counting carbon content which may be provided by esterified hydroxy groups. Esterified hydroxy-steroids are included within the scope of the invention, but the carbon content contributed by the acid moiety of the ester is not considered part of the essential carbon content of the steroid.

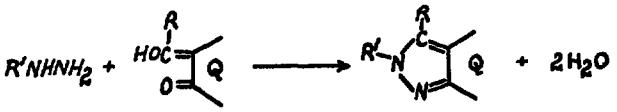
[*Price 4s. 6d.*]

The steroid moiety can be any member of the estrane, androstane, etiocholane, pregnane or allopregnane series. The foregoing can contain varying degrees of unsaturation and a variety of substituents in the form of hydrocarbon radicals or functional groups conventionally employed in the steroid art. Representative of the steroid moieties which make up the compounds of the invention are those having at position 17 a hydroxy, acyloxy, oxo, or both a hydroxy and a lower-alkyl radical, characteristic of the androgenic and anabolic steroids; or a lower-alkenyl, lower-alkynyl, acetyl, hydroxyacetyl, 1,2-dihydroxyethyl or 1-hydroxyethyl radical, optionally together with a hydroxy group at C_{17}, characteristic of the progestational and adrenal cortical steroids. Except where otherwise indicated, the lower-alkyl, lower-alkenyl, lower-alkynyl and lower-alkanoyl radicals mentioned herein contain up to six carbon atoms. The steroid moiety can also have one or more substituents at other positions of the nucleus as is possible with compounds of this type, for example, hydroxy or oxo radicals at position 11; halogen atoms, preferably fluorine, at the 9-position; and lower-alkyl groups at the 4- and 6-positions. The steroid moiety can also have one or more double bonds at the 4,5- and/or 6,7-positions. The steroid moiety preferably possesses angular methyl groups at C_{10} or C_{13}, although 18- and 19-nor-steroids, lacking one of the angular methyl groups at C_{13} and C_{10}, respectively, are also contemplated.

When acyloxy radicals are present in the steroid moiety, the acyl radicals are preferably derived from carboxylic acids having from one to ten carbon atoms, conventionally employed in the steroid art, and having a molecular weight less than 250. Representative of the acyl radicals which can be present are lower-alkanoyl radicals, e.g., formyl, acetyl, propionyl, butyryl, isobutyryl, caproyl, heptanoyl, octanoyl or trimethylacetyl; carboxy-lower-alkanoyl radicals, e.g., succinyl (β-

carboxypropionyl); cycloalkyl-lower-alkanoyl radicals, e.g., β-cyclopentylpropionyl or β-cyclohexylpropionyl; monocarbocyclic aroyl radicals, e.g., benzoyl, *p*-toluyl, *p*-nitrobenzoyl or 3,4,5-trimethoxybenzoyl; monocarbocyclic aryl-lower-alkanoyl or -alkenoyl radicals, such as phenylacetyl, β-phenylpropionyl or cinnamoyl; and monocarbocyclic aryloxy-lower-alkanoyl radicals, such as *p*-chlorophenoxyacetyl.

The compounds of the invention are prepared by reacting a 2 - (1 - hydroxyalkylidene) - 3 - oxo - steroid with a hydrazine, in particular, hydrazine itself or a mono-substituted hydrazine in which the substituent is inert to the reaction according to the following equation:



I II

In the above general formulas I and II, Q represents the remaining portion of the steroid moiety described above.

In the above formulas I and II, R represents a hydrogen atom or a lower-alkyl radical, the latter having preferably from one to four carbon atoms, thus including such groups as methyl, ethyl, propyl, isopropyl, or butyl.

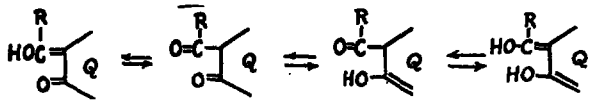
In the above formula II, R^1 represents a hydrogen atom or a substituent inert under the conditions of the reaction between the hydrazine and 2 - (1 - hydroxyalkylidene)-steroid. A preferred group of substituents includes lower-alkyl radicals, e.g., methyl, ethyl, propyl, isopropyl or butyl; monocarbocyclic aryl radicals, e.g., phenyl or *p*-tolyl; lower-alkanoyl radicals, e.g., acetyl, propionyl or butyryl; monocarbocyclic aroyl radicals, e.g., benzoyl, *p*-nitrobenzoyl or *p*-toluyl; monocarbocyclic aryl - lower - alkanoyl radicals, e.g., phenylacetyl, β-phenylpropionyl or *p*-chlorophenylacetyl; monocarbocyclic aryloxy - lower-alkanoyl radicals, e.g., phenoxyacetyl, *p*-chlorophenoxyacetyl or *p*-methoxy-phenoxyacetyl; and the carbamyl and guanyl radicals. When compounds where R^1 represents acyl, carbamyl or guanyl radicals, the starting mono-substituted hydrazines are mono-acyl hydrazines, semicarbazide or aminoguanidine, respectively. Alternatively, the compounds wherein R^1 represents hydrogen can be utilized as intermediates for preparing the compounds wherein R^1 represents an acyl radical or the carbamyl radical by reacting said compounds wherein R^1 represents hydrogen with the appropriate carboxylic acid anhydride, or with cyanic acid (an alkali metal cyanate in the presence of mineral acid), respectively.

In the above formula II, the radical R^1 is attached to one of the nitrogen atoms of the pyrazole ring, forming one of two possible isomeric structures (IIa and IIb):



IIa IIb

It is not known which of these two forms is produced in a given instance, and there is evidence that in some cases both isomers are obtained. This is due to the fact that the 2-hydroxy-alkylidene-3-oxo-steroid (I) in solution exists in tautomeric equilibrium, viz.:



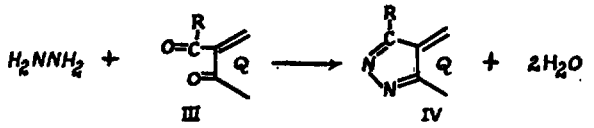
so that the substituted nitrogen portion of the hydrazine (R^1NH—) can react with either the substituent in the 2-position or the substituent in the 3-position of the steroid nucleus. For this reason the chemical formulae and nomenclature used herein are intended, unless otherwise stated, to relate to any of these tautomeric forms in the case of reactants and products.

It has, however, been established that the reaction of the 2 - hydroxyalkylidene - 3-oxo - steroid with methylhydrazine ($R^1 = CH_3$) gives predominantly the 1^1 - methylpyrazole derivative (form IIa). This was proved by reacting a given 2 - hydroxyalkylidene - 3-oxo - steroid with methylsemicarbazide, $H_2NN(CH_3)CONH_2$, followed by cyclization by pyrolysis of the resulting 3 - oxo - steroid substituted in the 2 - position by the radical, $H_2NCON(CH_3)NHCH=$, to give a pyrazole of type IIb where the methyl group is unequivocally in the 2^1-position. The latter compound proved to be different from the compound produced by reacting the same 2-hydroxyalkylidene - 3 - oxo - steroid with methylhydrazine.

The condensation of the hydrazine or substituted hydrazine with a 2-hydroxyalkylidene-

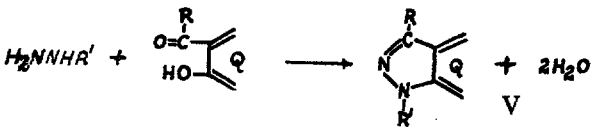
3 - oxo - steroid is carried out by heating said steroid with at least one molar equivalent of the hydrazine in an inert solvent at a temperature between about 50° C. and 150° C. The inert solvent is preferably a lower-alkanol, e.g., ethanol.

If the steroid moiety has a double bond already present in the 1,2-position, the essential steroid intermediate is a 2-formyl-Δ^1-steroid (III; R is H) or a 2-lower-alkanoyl-Δ^1-steroid (III; R is a lower-alkyl). If the hydrazine reactant is hydrazine itself (R^1 is H), the reaction is represented by the following equation :



III IV

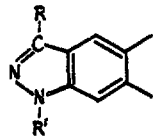
If the hydrazine reactant is a substituted hydrazine, the reaction is represented by the following equation:



V

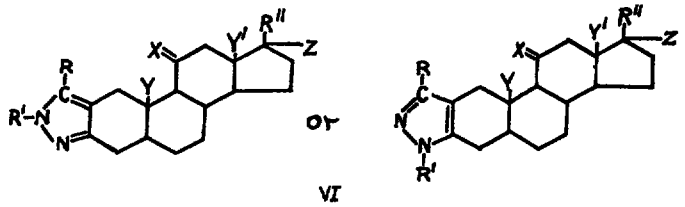
The intermediate 2 - acyl - Δ^1 - steroid (III) can be prepared by bromination or chlorination of a 2 - acyl steroid (I) in the 2-position, followed by dehydrohalogenation with collidine or with lithium chloride in dimethylformamide solution.

Compounds having an aromatic ring A characteristic of the estrogens (estratriene compounds), viz.:



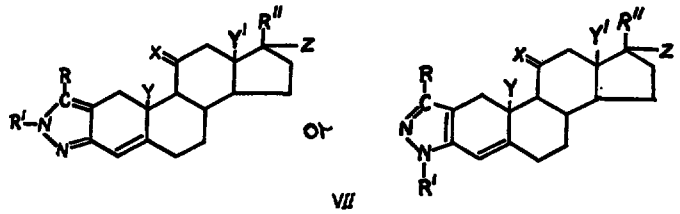
can be prepared by dehydrogenation of the corresponding Δ^4 - 19 - nor - steroidopyrazole by conventional procedures, as by heating with palladium-on-carbon catalyst.

A particularly preferred group of compounds comprises those having the structural formula

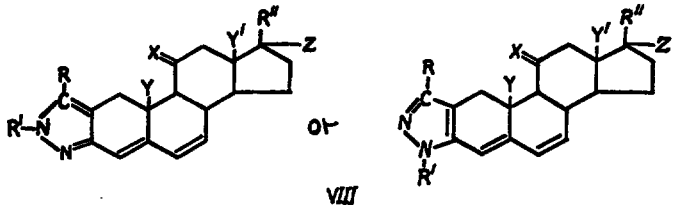


VI

wherein R represents hydrogen or a lower-alkyl radical; R^1 represents hydrogen or a lower-alkyl, monocarbocyclic aryl, lower-alkanoyl, monocarbocyclic aryloxy-lower-alkanoyl, the carbamyl or the guanyl radical; R^{11} represents hydrogen or a lower-alkyl radical, a lower-alkenyl radical, a lower-alkynyl radical, the acetyl radical, a ketalized acetyl radical, the hydroxyacetyl radical, a ketalized hydroxyacetyl radical, the 1,2-dihydroxyethyl radical or the 1-hydroxyethyl radical; X represents H_2, (H) (OH) and O; Y and Y^1 represent hydrogen or the methyl radical, at least one being methyl; and Z represents hydrogen or the hydroxy radical, Z being restricted to hydroxy when R^{11} represents hydrogen, or a lower-alkyl, lower-alkenyl or lower-alkynyl radical. Also contemplated are carboxylic acid esters of the foregoing compounds of the type referred to above, as well as those having one double bond in the 4,5-position (VII), or two double bonds, one in the 4,5-position and the other in the 6,7-position (VIII).



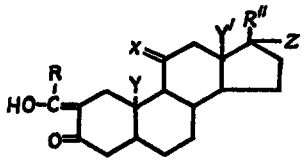
VII



VIII

In the above general formulas VI, VII and VIII, R^{11}, when it represents a lower-alkyl, lower-alkenyl, or lower-alkynyl radical, preferably has from one to four carbon atoms and may be straight or branched, and thus includes such groups as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary-butyl, vinyl, 1-propenyl, 2-propenyl, ethynyl or propargyl.

The compounds of formulas VI, VII and VIII are prepared by reacting the appropriate 2 - (1 - hydroxyalkylidene) - 3 - oxo - steroid, viz.:



IX

or the corresponding compounds where double bonds are present in the 4,5- or the 4,5 and 6,7-positions, with a hydrazine compound R^1NHNH_2; R, R^1, R^{11}, X, Z, Y and Y^1 having the same meanings given above, except that when the steroid moiety contains oxo groups in addition to the one at position 3, they are preferably protected as a ketal derivative to prevent side reactions with the hydrazine (hydrazone formation). For example, when compounds in which R^{11} represents acetyl or hydroxyacetyl are desired, these radicals are preferably ketalized by known methods, e.g., with ethylene glycol, prior to introduction of the hydroxyalkylidene radical at the 2-position and reaction with a hydrazine. The 20-monoketals of 3,20 - dioxo - steroids are prepared from the 3,20 - diketals by selective hydrolysis by known methods, e.g., by allowing the diketal to stand at room temperature in acetone solution containing a trace of *p*-toluenesulfonic acid. The ketal groups are readily cleaved by dilute acid either before or after the condensation with a hydrazine. It has been found, however, that 3,20 - dioxo-steroids bearing hydroxy groups at the 17- and 21-positions can be selectively formylated in the 2-position without protecting the 20-oxo group by ketalization, particularly if the 21-hydroxy group is etherified with a trityl or pyranyl radical. An oxo group at the 11-position is relatively unreactive and need not be protected before reaction with hydrazine or a derivative thereof.

As a variant on ketal formation, in the case where R^{11} is hydroxyacetyl and Z is OH, characteristic of cortisone and related cortical hormones, the side chain can be protected against formylation by first converting the compound to the 17,20;20,21 - bismethylenedioxy derivative by reacting it with formaldehyde in the presence of strong acid by known methods.

The compounds of the invention are useful as intermediates in the preparation of different species within the scope of the invention by introduction of new groups or alteration of groups already present in the steroid nucleus by known methods. For example, a steroido-[3.2-c] pyrazole having a hydroxy group in the 17-position of the steroid nucleus and a carbamyl group on the pyrazole ring (VI, VII or VIII; R^1 is $CONH_2$, R^{11} is H, Z is OH) can be oxidized to the corresponding 17-oxo compound and the latter reacted with potassium acetylide to give the 17-ethynyl-17-hydroxy derivative (VI, VII or VIII; R^{11} is $CH{\equiv}C-$, Z is OH). As another instance, a steroido - [3.2-c] pyrazole having a 1-hydroxyethyl radical in the 17-position (VI, VII or VIII; R^{11} is $CH_2CH(OH)-$, Z is H) can be oxidized to the corresponding 17-

acetyl compound (VI, VII or VIII; R^{11} is CH_3CO—, Z is H). The unsubstituted pyrazole ring (VI, VII or VIII; R, R^1 are H) is sensitive to oxidizing agents; therefore, it is preferable to employ the N-carbamyl derivatives (R^1 is $CONH_2$) if it is desired to oxidize some portion of the steroid moiety.

The intermediate 2 - hydroxyalkylidene - 3-oxo - steroids (I), as described and claimed in our Application No. 33126/60 (Serial No. 911,815), are prepared by condensing a 3-oxo-steroid, a 3-oxo-Δ^4-steroid, or a 3-oxo-$\Delta^{4,6}$-steroid with a lower-alkyl lower-alkanoate, $RCOOR^{111}$, wherein R is hydrogen or lower-alkyl and R^{111} is lower-alkyl in the presence of a strong alkali metal base under anhydrous conditions. The strong base is preferably an alkali metal lower-alkoxide, amide or hydride. An acyl group enters the 2 - position with elimination of a molecule of an alcohol as follows:



Steroido [3.2-c] pyrazoles saturated at the 5-position and belonging to the normal series (ring juncture A/B *cis*, etiocholane series) are also contemplated as well as those belonging to the allo series (ring juncture A/B *trans*, androstane series). Although, by analogy with halogenation procedures, it would be expected that ring A saturated compounds of the etiocholane series (ring juncture A/B *cis*) would form 4 - hydroxy - alkylidene derivatives rather than 2 - hydroxyalkylidene derivatives, it has been found that the latter are produced preponderantly. This was proved by hydrogenating the double bond of a Δ^4-steroido [3.2-c] pyrazole to produce a mixture of saturated steroido [3.2-c] pyrazoles of the androstane and etiocholane series, and showing that the etiocholane isomer was identical with that produced by direct formation of the pyrazole from the hydroxymethylene derivative of the parent etiocholane compound. If the hydroxymethylene group had entered the 4-position, the resulting pyrazole would have been fused to the 3,4-position of the steroid nucleus and would have been different from the etiocholane pyrazole obtained by hydrogenation of the Δ^4 compound. Therefore, etiocholane as well as androstane compounds are useful as starting materials in the preparation of the compounds of the invention.

Pyrazoles are weakly basic substances and will form acid-addition salts upon addition of strong acids and quaternary ammonium salts upon addition of esters of strong acids.

The quaternary ammonium salts of the compounds of the invention are prepared by reacting a steroido [3.2-c]pyrazole with an ester of a strong inorganic or organic sulfonic acid, said ester preferably having a molecular weight less than about 200. A particularly preferred class of esters, because of their ready availability, are lower-alkyl, lower-alkenyl and monocarbocyclic aryl - lower - alkyl esters, for example, methyl iodide, ethyl iodide, ethyl bromide, propyl bromide, butyl bromide, allyl bromide, methyl sulfate, methyl benzenesulfonate, methyl *p*-toluenesulfonate, benzyl chloride and *o*-chlorobenzyl chloride. The reaction of the steroido [3.2-c] pyrazole and the quaternizing agent takes place upon simple admixture of the components, preferably in the presence of an inert organic solvent, although heating may be applied to accelerate the reaction.

The acid-addition and quaternary ammonium salts preferably have anions which are pharmacologically acceptable, that is, the anions did not appreciably increase the toxicity of the compound as a whole toward animal organisms. Such anions include, for example, the chloride, bromide, iodide, sulfate or acid sulfate, methanesulfonate or benzenesulfonate. Salts having toxic anions are, however, useful in that they serve as characterizing derivatives of the steroido [3.2-c] pyrazoles, and serve as intermediates for non-toxic quaternary salts by conventional ion exchange reactions. All acid-addition salts, regardless of the nature of the anions, are useful as intermediates in the purification of the free bases.

Endocrinological studies of the steroido [3.2-c] pyrazoles of the invention have shown that they possess useful metabolic, hormonal or anti-hormonal properties. In particular, they exhibit one or more of the following activities: anabolic, androgenic, pituitary inhibiting, estrogenic, progestational and adrenal cortical.

The steroido [3.2-c] pyrazoles of the invention, especially those having a saturated steroid nucleus and hydroxy and lower-alkyl radicals in the 17-position, further possess advantages in being anabolic (myotrophic and nitrogen retentive) at dose levels at which they do not show an appreciable degree of sex hormonal properties. For example, 17β-hydroxy - 17α - methylandrostano [3.2-c] pyrazole was found to have an anabolic activity in rats about thirty-five times that of 17α-methyltestosterone upon oral administration while having an androgenic activity only about one-fourth that of 17α - methyltestosterone. Anabolic agents are useful in the treatment of conditions arising from poor nitrogen utilization; various debilitating diseases; bone conditions such as fractures, osteoporosis, osteogenesis imperfecta: degenerative joint diseases; traumatic injuries which bring about losses of large amounts of nitrogen, such as severe burns and hypochromic anemias.

Generally speaking, the known anabolic agents possess a moderate to high degree of androgenic activity and their use leads to undesirable side-effects such as virilism and hirsutism. Therefore, the separation of these activities, are found in the compounds of the present invention, which have high anabolic but low androgenic activities, is a highly desirable feature.

Some of the steroido [3.2-c] pyrazoles of the invention, especially those having a bond in the 4.5-position of the steroid nucleus and hydroxy and lower-alkyl radicals in the 17-position, in addition to myotrophic activity further possess useful pituitary inhibiting and estrogenic activity. For example, 17β-hydroxy - 17α - methyl - 4 - androsteno [3.2-c] pyrazole was found to have a surprising degree of pituitary inhibiting activity not to be expected from its low androgenic activity and moderate estrogenic activity. Pituitary inhibiting agents are useful in the treatment of endocrinological disorders such as menopausal syndrome, endometriosis, postpartum breast engorgement, benign prostatic hypertrophy, functional uterine bleeding, chronic cystic mastitis, and suppression or termination of reproduction processes.

The compounds of the invention can be prepared for use by dispersing them in an aqueous suspension or by dissolving them in a pharmacologically acceptable oil or oil-water emulsion for parenteral administration; or by incorporation in tablet form with excipients for oral administration.

An especial advantage of the steroido [3.2-c] pyrazoles of the invention lies in the fact that they are particularly effective upon oral administration.

The structure of the compounds of the invention was established by the mode of synthesis, their ultraviolet and infrared spectra, and by the fact that the values found upon elementary analysis corresponded with the values calculated for the assigned structures.

The following examples will further illustrate the invention without the latter being limited thereby.

EXAMPLE 1.

(a) *2 - Hydroxymethylene - 17α - methylandrostan - 17β - ol - 3 - one.*

A solution of 20.7 g. of 17α - methylandrostan - 17β - ol - 3 - one in 500 ml. of benzene was added to sodium methoxide (prepared by dissolving 15.0 g. of sodium in 250 ml. of absolute methanol, concentrating the solution and drying the residue for one hour at 150—160° C. and 15 mm.). Ethyl formate (48.8 g.) was then added with stirring in a nitrogen atmosphere. The reaction mixture was stirred for four hours longer at room temperature, allowed to stand for about fifteen hours, stirred for two hours longer and then poured into water. The benzene layer was separated and the aqueous layer extracted with benzene. Nitrogen was bubbled through the aqueous layer to remove benzene, and the mixture was filtered. Concentrated hydrochloric acid and ice were added to the filtrate until the mixture was acid to Congo Red, and the product was extracted with chloroform. The chloroform extracts were washed with water, dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to a volume of 80 ml., whereupon there separated 14.89 g. of 2-hydroxymethylene - 17α - methlyandrostan-17β - ol - 3 - one, m.p. 179—183° C. (uncorr.). A sample when recrystallized from an ether-methanol mixture and dried at 80° C. *in vacuo* had the m.p. 185—190.5° C. (corr.), $[\alpha]_D^{25} = +22.3°$ (1% in chloroform); ultraviolet maximum at 282 mμ (E = 10,300).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70.
Found: C, 76.10; H, 9.53.

2 - Hydroxymethylene - 17α - methylandrostan - 17β - ol - 3 - one, when heated with a molar equivalent amount of diethylamine, gave the diethylamine salt in the form of colorless plates, m.p. 114.6—116.4° C. (dec.) (corr.), $[\alpha]_D^{25}$ + 16.6° (1% in chloroform).

Anal. Calcd. for $C_{21}H_{32}O_3 \cdot (C_2H_5)_2NH$: C, 74.03; H, 10.69; N, 3.45.
Found: C, 74.24; H, 10.93; N, 3.20.

2 - Hydroxymethylene - 17α - methylandrostan - 17β - ol - 3 - one was found to possess significant pituitary inhibitory activity as measured by the enhancement of estrogen induced testicular atrophy in rats at dose levels of 10—20 mg./kg./day.

(b) *17β - Hydroxy - 17α - methylandrostano [3.2-c] pyrazole* [VI; R and R^1 are H, R^{11} is CH_3, X is H_2, Z is OH, Y and Y^1 are CH_3].

To a warmed solution of 500 mg. of 2-hydroxy - methylene - 17α - methylandrostan-

17β - ol - 3 - one in 40 ml. of 95% ethanol was added 160 mg. of hydrazine hydrate. The reaction mixture was refluxed for three hours, concentrated to a volume of 20 ml., cooled and the product which separated was collected and washed with ether, giving 440 mg., m.p. 144° C. (uncorr.).

The reaction was repeated starting with 3.50 g. of 2 - hydroxymethylene - 17α-methylandrostan - 17β - ol - 3 - one and 1.12 g. of hydrazine hydrate in 200 ml. of ethanol, giving 3.33 g. of crude product. The combined products were recrystallized from 400 ml. of acetone to give 3.26 g. of product, m.p. 146—148° C. (uncorr.). All of the crude material was combined, dissolved in 200 ml. of 95% ethanol, 2 ml. of hydrazine hydrate was added and the mixture refluxed for four hours. The reaction mixture was concentrated to dryness and the residue recrystallized twice from ethanol and dried at 150° C. for eight hours *in vacuo*, giving 17β - hydroxy - 17α - methylandrostano [3.2-c] pyrazole, m.p. 230—242° C. (corr.), $[\alpha]_D^{25} = +35.7 \pm 0.2°$ (1% in chloroform); ultraviolet maximum at 223 mμ (E = 4,740).

Anal. Calcd. for $C_{21}H_{32}N_2O$: C, 76.78; H, 9.82; N, 8.53.
Found: C, 76.65; H, 9.73; N, 8.45.

EXAMPLE 2.

17β - Hydroxy - 17α - methylandrostano [3.2-c] pyrazole [VI; R and R^1 are H, R^{11} is CH_3, X is H_2, Z is OH, Y and Y^1 are CH_3].

17α-Methylandrostan - 17β - ol - 3 - one (49.54 g.) was dissolved in 1600 ml. of benzene, 400 ml. of the benzene was distilled off and the solution cooled to room temperature. There was then added 25.0 g. of sodium hydride and 60 ml. of ethyl formate (previously dried and distilled over phosphorus pentoxide), while maintaining the reaction mixture under a nitrogen atmosphere. Methanol (40 ml.) was then slowly added while the mixture was cooled in an ice bath. The reaction mixture was allowed to come to room temperature and stirred for eighteen hours in a nitrogen atmosphere. Methanol (5 ml.) was then added, and the mixture stirred for ten minutes and cooled in an ice bath. Water was added, the suspended solid material was collected by filtration, washed with ethyl acetate and mixed with the aqueous portion of the filtrate, and the latter was treated with concentrated hydrochloric acid and ice until the mixture was acidified. The resulting solid product was collected by filtration, washed with water and dried *in vacuo* first over solid potassium hydroxide and then over calcium chloride at 50° C. for three days, giving 51.6 g. of 2-hydroxymethylene - 17α - methylandrostan - 17β - ol-3 - one, m.p. 158—179° C. (uncorr.). The latter material was dissolved in 600 ml. of 95% methanol, the solution filtered, and 8.4 ml. of hydrazine hydrate was added to the filtrate. The latter mixture was refluxed for ten minutes, concentrated to a volume of 250 ml. and cooled, whereupon there separated 47.0 g. of 17β - hydroxy - 17α - methylandrostano [3.2-c] pyrazole, m.p. 213—228° C. (uncorr.). Upon concentration of the mother liquors a second crop of 3.69 g. was obtained. The combined product had the m.p. 225—241° C. (uncorr.) when recrystallized from ethanol and dried over phosphorus pentoxide for thirty-one hours at 100—130° C.

A solution of 17β - hydroxy - 17α - methylandrostano - [3.2-c] pyrazole in 350 ml. of methanol was treated with 35 ml. of 1.11*M* ethereal hydrogen chloride. Upon concentration of the solution there was obtained the hydrochloride salt of 17β - hydroxy - 17α-methylandrostano [3.2-c] pyrazole in solvated form, m.p. 234—254° C. (uncorr.).

When measured by nitrogen retention studies in the rat, 17β - hydroxy - 17α - methylandrostano [3.2-c] pyrazole was found to have an anabolic activity about thirty-five times that of 17α - methyltestosterone upon oral administration while having an androgenic activity only about one-fourth that of 17α-methyltestosterone.

EXAMPLE 3.

17β - Hydroxy - 17α - methylandrostano [3.2-c] - N - acetylpyrazole [VI; R is H, R^1 is $COCH_3$, R^{11} is CH_3, X is H_2, Z is OH, Y and Y^1 are CH_3].

A mixture of 8 g. of 17β - hydroxy - 17α-methylandrostano-[3.2-c] pyrazole (Examples 1 and 2) and 6 ml. of acetic anhydride in 80 ml. of pyridine was allowed to stand at room temperature for about fifteen hours. The reaction mixture was poured into 1 liter of ice water and the resulting precipitate was collected by filtration. The solid product was recrystallized twice from ethanol and dried for eighteen hours at 30° C. and for twenty-four hours *in vacuo* at room temperature, to give 17β - hydroxy - 17α - methylandrostano [3.2-c] - N - acetylpyrazole, m.p. 111.5—115.5° C. (dec.) (corr.), containing one mole of ethanol of crystallization; $[\alpha]_D^{25} = +43.1 \pm 0.1°$ (1% in chloroform); ultraviolet maximum at 258 mμ (E = 19,000).

Anal. Calcd. for $C_{23}H_{34}N_2O_2 \cdot C_2H_5OH$: C, 72.07; H, 9.68; N, 6.73.
Found: C, 72.40; H, 9.78; N, 6.72.

When tested for myotrophic and nitrogen retention activity in the rat, 17β - hydroxy-17α - methylandrostano - [3.2-c] - N - acetylpyrazole exhibited anabolic and androgenic activities about equal to those of 17β-hydroxy - 17α - methylandrostano [3.2-c]-pyrazole. It also exhibited significant estrogenic activity.

EXAMPLE 4.

17β - Hydroxy - 17α - methylandrostano [3.2-c] - 1¹ - methyl - pyrazole [VI; R is H, R¹ and R¹¹ are CH_3, X is H_2, Z is OH, Y and Y¹ are CH_3].

A solution of 1.52 g. of methylhydrazine sulfate and 1.97 g. of fused sodium acetate in 80 ml. of water was added to a solution of 3.33 g. of 2 - hydroxymethylene - 17α - methylandrostan - 17β - ol - 3 - one (Example 1, part (a)) in 400 ml. of 95% ethanol. The mixture was heated on a steam bath for thirty minutes and then diluted with 700 ml. of ethyl acetate and 500 ml. of water. The mixture was well shaken and the ethyl acetate layer was separated and washed with water. The water was in turn washed with ethyl acetate and the combined ethyl acetate extracts were dried over anhydrous sodium sulfate and concentrated *in vacuo*. The residue was dissolved in 300 ml. of acetone containing a small amount of methanol and the solution was concentrated to a volume of 150 ml., whereupon there was obtained in two crops 1.72 g. of 17β - hydroxy - 17α - methylandrostano [3.2-c] - 1¹ - methylpyrazole, m.p. 234—248° C. (uncorr.), and 0.48 g., m.p. 223—248° C. (uncorr.). After successive recrystallization from ethyl acetate and methanol and drying at 90° C. *in vacuo* for eight hours, there was obtained a sample having the m.p. 249.5—259° C. (corr.), $[\alpha]_D^{25} = +39.0 \pm 0.1°$ (1% in 95% ethanol); ultraviolet maximum at 231 mμ (E = 7,050).

Anal. Calcd. for $C_{22}H_{34}N_2O$: C, 77.14; H, 10.01; O, 4.67.
Found: C, 77.44; H, 9.90; O, 4.90.

A mixture of 1.85 g. of 17β - hydroxy - 17α - methylandrostano [3.2-c] - 1¹ - methylpyrazole and 10 ml. of methyl iodide in 10 ml. of methanol was allowed to stand at room temperature for sixty-three hours. The mixture was then heated at 100° C. for one hour, cooled and concentrated to dryness. The residue was recrystallized repeatedly from methanol and finally from acetonitrile. There was thus obtained the methiodide salt of 17β-hydroxy - 17α - methylandrostano [3.2-c]-1¹ - methylpyrazole in the form of colorless massive prisms, m.p. 282.4—291.2° C., (dec.) (corr.); $[\alpha]_D^{25} = +35.8 \pm 0.4°$ (0.5% in methanol).

Anal. Calcd. for $C_{23}H_{37}IN_2O$: C, 57.01; H, 7.70; I, 26.20.
Found: C, 57.09; H, 7.67; I, 25.87.

EXAMPLE 5.

17β - Hydroxy - 17α - methylandrostano [3.2-c] - N - phenylpyrazole [VI; R is H, R¹ is C_6H_5, R¹¹ is CH_3, X is H_2, Z is OH, Y and Y¹ are CH_3].

A solution of 3.33 g. of 2-hydroxymethylene-17α - methylandrostan - 17β - ol - 3 - one (Example 1, part (a)) and 1.10 g. of phenylhydrazine in 100 ml. of methanol was gradually concentrated on a steam bath to a volume of about 50 ml. over a period of about three hours. The reaction mixture was cooled, and the product which separated was collected by filtration and recrystallized from methanol, giving 17β - hydroxy - 17α - methylandrostano [3.2-c] - N - phenylpyrazole containing 1 mole of methanol of crystallization, m.p. indefinite, starting at 99.5° C. (corr.), $[\alpha]_D^{25} = +55.0 \pm 0.2°$ (1% in chloroform); ultraviolet maximum at 262 mμ (E = 14,000).

Anal. Calcd. for $C_{27}H_{36}N_2O \cdot CH_3OH$: C, 77.02; H, 9.23; O, 7.33.
Found: C, 76.90; H, 8.96; O, 7.25.

EXAMPLE 6.

(a) *2 - Hydroxymethyleneandrostan - 17β - ol-3 - one* was prepared by following the procedure of Example 1(a); m.p. indefinite, starting at 199.5° C. (corr.), $[\alpha]_D^{25} = +48.7 \pm 0.2°$ (1% in chloroform); ultraviolet maximum at 277 mμ (E = 11,100); infrared maxima (potassium bromide cell) at 2.96, 6.02, 6.39, 6.82 and 6.92 μ.

(b) *17β - Hydroxyandrostano [3.2-c] pyrazole* [VI; R, R¹ and R¹¹ are H, X is H_2, Z is OH, Y and Y¹ are CH_3] was prepared by following the procedure of Example 5; m.p. 127.5—128.5° C. (dec.) (corr.), $[\alpha]_D^{25} = +55.1 \pm 0.2°$ (1% in chloroform).

EXAMPLE 7.

17β - Propionoxyandrostano [3.2-c] pyrazole [VI; R, R^1 and R^{11} are H, X is H_2, Z is $OCOC_2H_5$, Y and Y^1 are CH_3].

A solution of 1.00 g. of 2 - hydroxymethyleneandrostan - 17β - ol - 3 - one (Example 6, part (a)) in 100 ml. of propionic acid was heated to 70° C. Hydrazine sulfate (0.76 g.) was added and the reaction mixture was stirred for two hours. Additional propionic acid (50 ml.) was added and the mixture stirred for seventy-two hours at 70° C. After this time, 100 ml. of water was added and the mixture stirred until solution was complete. Additional water (200 ml.) was then added, and the reaction mixture was cooled and extracted with ether. The ether extracts were washed with 10% sodium bicarbonate solution (400 ml.), dried over anhydrous sodium sulfate and concentrated. The residue was dissolved in 3 ml. of ether, 1 ml. of pentane was added, and the solution cooled in ice to give 0.83 g. of 17β-propionoxyandrostano [3.2-c] pyrazole, m.p. 82—100° C., which then resolidified and remelted at 170—178° C. (uncorr.). A sample when recrystallized from an ether-pentane mixture and then from ether, and dried *in vacuo* at 45° C. for eight hours, had the m.p. 181—195° C. (corr.), $[\alpha]_D^{25} = +40.2 \pm 0.1°$ (1% in chloroform); ultraviolet maximum at 223 mμ (E = 4,900).

Anal. Calcd. for $C_{23}H_{34}N_2O_2$: C, 74.55; H, 9.25; O, 8.64.
Found: C, 74.45; H, 9.28; O, 8.30.

EXAMPLE 8.

(a) *17α - Ethyl - 2 - hydroxymethyleneandrostan - 17β - ol - 3 - one* was prepared by following the procedure of Example 1(a) and used directly to prepare

(b) *17α - Ethyl - 17β - hydroxyandrostano [3.2-c] pyrazole* [VI; R and R^1 are H, R^{11} is C_2H_5, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. 249—251.5° C. (corr.), $[\alpha]_D^{25} = +32.7 \pm 0.2°$ (1% in chloroform); ultraviolet maximum at 224 mμ (E = 5,100).

EXAMPLE 9.

(a) *2 - Hydroxymethylene - 4 - androsten-17β - ol - 3 - one* was prepared from 25 g. of testosterone, 7.5 g. of sodium hydride and 25 ml. of ethyl formate in 500 ml. of dry benzene according to the manipulative procedure described above in Example 2. There was thus obtained 21.63 g. of 2 - hydroxymethylene - 4 - androsten - 17β - ol - 3 - one in crystalline form.

(b) *17β - Hydroxy - 4 - androsteno [3.2-c] pyrazole* [VII; R, R^1 and R^{11} are H, X is H_2, Z is OH, Y and Y^1 are CH_3] was prepared from 2.5 g. of 2 - hydroxymethylene - 4 - androsten - 17β - ol - 3 - one and 1.7 g. of hydrazine hydrate in 80 ml. of methanol according to the manipulative procedure described above in Example 5. The crude product was recrystallized from methanol and dried for sixteen hours at 120° C., giving 17β-hydroxy - 4 - androsteno [3.2-c] pyrazole, m.p. 227—240° C. (uncorr.) with previous softening.

(c) *17β - Hydroxy - 4 - androsteno [3.2-c] pyrazole - N - carboxamide* [VII; R is H, R^1 is $CONH_2$, R^{11} is H, X is H_2, Z is OH, Y and Y^1 are CH_3].

17β - Hydroxy - 4 - androsteno [3.2-c] pyrazole (5 g. as obtained in part (b) above) was dissolved in 200 ml. of methanol and water (50 ml.) was added until precipitation began. Methanol (10 ml.) was added and the solution warmed until the steroid was completely redissolved. The solution was cooled and 15 ml. of ethereal hydrogen chloride containing 0.016 mole of hydrogen chloride was added, followed by 1.3 g. of potassium cyanate in about 3 ml. of water. The desired product precipitated immediately, and it was collected by filtration and recrystallized three times from methanol giving 17β - hydroxy-4 - androsteno [3.2-c] pyrazole - N - carboxamide, m.p. 221.5—228° C. (corr.), $[\alpha]_D^{25} = +83.4 \pm 0.1°$ (1% in pyridine); ultraviolet maxima at 236 and 280 mμ (E = 8,500 and 23,600, respectively).

Anal. Calcd. for $C_{21}H_{29}N_3O_2$: C, 70.95; H, 8.22; N, 11.82.
Found: C, 71.08; H, 8.37; N, 12.19.

EXAMPLE 10.

17β - Hydroxy - 4 - androsteno [3.2-c] pyrazole [VII; R, R^1 and R^{11} are H, X is H_2, Z is OH, Y and Y^1 are CH_3].

A mixture of 1.1 g. of 17β - hydroxy - 4-androsteno - [3.2-c] pyrazole - N - carboxamide (Example 9, part (c)), 1.0 ml. of concentrated hydrochloric acid and 55 ml. of 95% ethanol was refluxed for four hours. The reaction mixture was cooled, 1 ml. of concentrated ammonium hydroxide was added and the mixture allowed to stand for ten minutes. Water was then added and the ethanol removed by concentration *in vacuo*. The re-

maining aqueous suspension was filtered to give 1.0 g. of 17β - hydroxy - 4 - androsteno [3.2-c] - pyrazole, m.p. 276—277° C. (uncorr.). Upon recrystallization from methanol and drying at 110° C. *in vacuo* there was obtained a sample having the m.p. 275—276.5° C. (corr.), $[\alpha]_D^{25} = +147.6 \pm 0.1°$ (1% in pyridine); ultraviolet maximum at 260 mμ (E = 10,970).

Anal. Calcd. for $C_{20}H_{28}N_2O$: C, 76.88; H, 9.03; N, 8.97.
Found: C, 76.86; H, 8.75; N, 9.37.

EXAMPLE 11.

17 - Oxo - 4 - androsteno [3.2-c] pyrazole-N - carboxamide.

A mixture of 8.0 g. of 17β - hydroxy - 4-androsteno - [3.2-c] pyrazole - N - carboxamide (Example 9) and 500 ml. of glacial acetic acid was stirred until partial solution had occurred. The mixture was then cooled to 14° C. in a water bath, and a solution of 3.2 g. of chromic oxide in 8 ml. of water and 24 ml. of glacial acetic acid was added dropwise during a period of ten minutes. The reaction mixture was stirred for five and one-half hours, an equal volume of water added, and the solid material which separated was collected by filtration, washed with water and dissolved in chloroform. The chloroform solution was filtered, concentrated to a small volume, and ether was added to cause crystallization of the product. There was thus obtained 4.83 g. of 17 - oxo - 4 - androsteno [3.2-c] pyrazole - N - carboxamide, m.p. 270—271° C. (uncorr.).

EXAMPLE 12.

17 - Oxo - 4 - androsteno [3.2-c] pyrazole was prepared by hydrolysis of the product of Example 11 according to the process of Example 10; m.p. 258.6—263.8° C. (corr.), $[\alpha]_D^{25} = +199.1 \pm 0.2°$ (1% in 95% ethanol); ultraviolet maximum at 261 mμ (E = 11,300).

EXAMPLE 13.

(a) *2 - Hydroxymethylene - 17α - methyl - 4-androsten - 17β - ol - 3 - one* was prepared by the procedure of Example 2; m.p. 178.5—180° C. (corr.), $[\alpha]_D^{28} = +14.0°$ (1% in chloroform); ultraviolet maxima at 252 and 307 mμ (E = 12,000 and 6,030, respectively).

(b) *17β - Hydroxy - 17α - methyl - 4 - androsteno [3.2-c] pyrazole* [VII; R and R^1 are H, R^{11} is CH_3, X is H_2, Z is OH, Y and Y^1 are CH_3] was prepared by following the procedure of Example 5; m.p. 248—258.5° C. (corr.), $[\alpha]_D^{25} = +132.6 \pm 0.2°$ (1% in pyridine); ultraviolet maximum at 261 mμ (E = 10,500); infrared maxima at 3.12, 3.43, 6.12, 6.65, 6.89 and 7.28 μ.

EXAMPLE 14.

(a) *2 - Hydroxymethylene - 17α - ethyl - 4-androsten - 17β - ol - 3 - one* was prepared by following the procedure of Example 2 and was used directly without further purification to prepare

(b) *17β - Hydroxy - 17α - ethyl - 4 - androsteno [3.2-c] pyrazole* [VII; R and R^1 are H, R^{11} is C_2H_5, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. 284.5—290.5° C. (corr.), $[\alpha]_D^{25} = +102.1 \pm 0.2°$ (1% in chloroform); ultraviolet maximum at 261 μ (E = 10,561).

EXAMPLE 15.

(a) *2 - Hydroxymethylene - 17α - vinyl - 4-androsten - 17β - ol - 3 - one* was prepared by following the procedure of Example 2 and used to prepare

(b) *17β - Hydroxy - 17α - vinyl - 4 - androsteno [3.2-c] pyrazole* [VII; R and R^1 are H, R^{11} is $CH=CH_2$, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. 247—259.5° C. (corr.), $[\alpha]_D^{25} = +101.2 \pm 0.2°$ (1% in chloroform); ultraviolet maximum at 260 mμ (E = 10,600).

EXAMPLE 16.

(a) *17α - Ethynyl - 2 - hydroxymethylene-4-androsten-17β-ol-3-one.*

To a solution of 14.2 g. of 17α - ethynyl - 4-androsten - 17β - ol - 3 - one in 300 ml. of dry pyridine was added 23 ml. of dry ethyl formate and then a solution of sodium ethoxide in ethanol (from 2.1 g. of sodium and 35 ml. of absolute ethanol). The reaction mixture was allowed to stand at room temperature for forty-two hours and then poured onto ice-water. Glacial acetic acid (218 ml.) was added and the gummy product was separated and dissolved in ether. The ether solution was washed with a solution of 30 g. of potassium hydroxide in 1.5 liters of water, and the aqueous layer was cooled to 5° C. and acidified with 6*N* hydrochloric acid. The precipitated product was collected by filtration and dried *in vacuo* over phosphorus pentoxide at 60° C., giving 13.5 g. of 17α - ethynyl - 2 - hydroxymethylene - 4 - androsten - 17β - ol-3 - one.

(b) *17α - Ethynyl - 17β - hydroxy - 4 - androsteno [3.2-c] pyrazole* [VII; R and R^1 are H, R^{11} is C≡CH, X is H_2, Z is OH, Y and Y^1 are CH_3] was prepared from 5.0 g. of 17α-ethynyl - 2 - hydroxymethylene - 4 - androsten - 17β - ol - 3 - one and 0.77 g. of hydrazine hydrate according to the manipulative procedure described above in Example 5. The resulting product was recrystallized from methanol and from aqueous acetone and dried

in vacuo at 115° C. for twenty-four hours, giving 17α - ethynyl - 17β - hydroxy - 4-androsteno [3.2-c] pyrazole, m.p. 239.6—246.6° C. (corr.); $[\alpha]_D^{25} = +29.0° \pm 0.1°$ (1% in chloroform); ultraviolet maximum at 261 mμ (E = 10,700). It had infrared bands at 3.10 μ and 4.77 μ, characteristic of an acetylene linkage.

Anal. Calcd. for $C_{22}H_{28}ON_2$: C, 78.53; H, 8.39.
Found: C, 78.51; H, 8.35.

EXAMPLE 17.

(a) *2 - Hydroxymethylene - 4 - pregnen - 20β-ol - 3 - one* was prepared by following the procedure of Example 2 and used to prepare (b) *20β - Hydroxy - 4 - pregneno [3.2-c] pyrazole* [VII; R and R^1 are H, R^{11} is $CH(OH)CH_3$, X is H_2, Z is H, Y and Y^1 are CH_3] by following the procedure of Example 1(b); m.p. 262.5—269° C. (corr.), $[\alpha]_D^{25} = +114.9 \pm 0.1°$ (1% in chloroform); ultraviolet maximum at 260 mμ (E = 11,000).

EXAMPLE 18.

20β - Hydroxy - 4 - pregneno [3.2-c] pyrazole - N - carboxamide [VII; R is H, R^1 is H_2NCO; R^{11} is $CH(OH)CH_3$, X is H_2, Z is H, Y and Y^1 are CH_3] was prepared by carbamylation of the product of Example 17(b) by the process of Example 9(c); m.p. 219.8—232.2° C. (corr.), $[\alpha]_D^{25} = +54.4 \pm 0.3°$ (0.5% in chloroform).

Anal. Calcd. for $C_{23}H_{33}N_3O_2$: C, 72.02; H, 8.67; N, 10.96.
Found: C, 71.82; H, 8.51; N, 11.14.

EXAMPLE 19.

(a) *20 - Oxo - 4 - pregneno [3.2-c] pyrazole-N-carboxamide* [VII; R is H, R^1 is H_2NCO, R^{11} is $COCH_3$, X is H_2, Z is H, Y and Y^1 are CH_3] was prepared by oxidation of the product of Example 18 by the process of Example 11; m.p. 226.4—234.4° C. (corr.); $[\alpha]_D^{25} = +156.4 \pm 0.2°$ (0.5% in chloroform); ultraviolet maxima at 225, 236, 242 and 279 mμ (E = 7,150, 8,000, 8,000 and 21,700, respectively), was prepared.

(b) *20 - Oxo - 4 - pregneno [3.2-c] pyrazole* [VII; R and R^1 are H, R^{11} is $COCH_3$, X is H_2, Z is H, Y and Y^1 are CH_3] was then prepared by hydrolysis of the product of Example 19(a) by the process of Example 10; m.p. 259.6—269.6° C. (corr.); $[\alpha]_D^{25} = +233.9°$ (1% in chloroform); ultraviolet maximum at 261 mμ (E = 13,000).

Anal. Calcd. for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28.
Found: C, 78.01; H, 8.66; N, 8.00.

20 - Oxo - 4 - pregneno [3.2-c] pyrazole was found to have a progestational activity about 4—8 times that of a 17-ethynyltestosterone when administered orally, as measured by the endometrial response in the rabbit.

EXAMPLE 20.

(a) *2 - Hydroxymethylene - 17α - methyl-4,6 - androstadien - 17β - ol - 3 - one* was prepared by following the procedure of Example 2; m.p. 117—123° C. (uncorr.).

(b) *17β - Hydroxy - 17α - methyl - 4,6-androstadieno [3.2-c] - pyrazole* [VIII; R and R^1 are H, R^{11} is CH_3, X is H_2, Z is OH, Y and Y^1 are CH_3] was then prepared by following the procedure of Example 5; m.p. 279—284° C. (corr.), $[\alpha]_D^{25} = -126.1 \pm 0.1°$ (1% in pyridine); ultraviolet maxima at 226, 232, 297 and 308 mμ (E = 9,194, 8,244, 24,329 and 18,355, respectively).

EXAMPLE 21.

(a) *2 - Hydroxymethylene - 4,6 - androstadien-17β - ol - 3 - one* was prepared by following the procedure of Example 2; m.p. 80—100° C. (uncorr.).

(b) *17β - Hydroxy - 4,6 - androstadieno [3.2-c] pyrazole* [VIII; R, R^1 and R^{11} are H, X is H_2, Z is OH, Y and Y^1 are CH_3] was prepared by following the procedure of Example 5; m.p. 272.8—277.0° C. (corr.), $[\alpha]_D^{25} = -137.2 \pm 0.1°$ (1% in ethanol); ultraviolet maxima at 220, 225, 232, 296 and 300 mμ (E = 7,600, 8,500, 7,800, 22,000 and 16,600, respectively).

EXAMPLE 22.

(a) *2 - Hydroxymethylene - 4,4,17α - trimethyl - 5 - androsten - 17β - ol - 3 - one* was prepared by following the procedure of Example 2 and used to prepare

(b) *17β - Hydroxy - 4,4,17α - trimethyl - 5-androsteno [3.2-c] -pyrazole;* m.p. 270.4—276.0° C. (corr.), $[\alpha]_D^{25} = -55.0 \pm 0.2°$ (1% in 95% ethanol); ultraviolet maximum at 223 mμ (E = 5,300) by following the procedure of Example 5.

EXAMPLE 23.

(a) *2 - Hydroxymethylene - 17α - methyl - 19-norandrostan - 17β - ol - 3 - one* was prepared by following the procedure of Example 2; m.p. 206.2—210.6° C. (corr.), $[\alpha]_D^{25} = +96.1 \pm 0.1°$ (1% in chloroform); ultraviolet maximum at 283 mμ (E = 7,800).

(b) *17β - Hydroxy - 17α - methyl - 19 - norandrostano [3.2-c] - pyrazole* [VI; R and R^1 are H, R^{11} is CH_3, X is H_2, Z is OH, Y is H, Y^1 is CH_3] was then prepared by following the procedure of Example 5; m.p. 140.4—152.4° C. (corr.), $[\alpha]_D^{25} = +90.0 \pm 0.1°$ (1% in chloroform); ultraviolet maximum at 224 mμ (E = 4,800).

EXAMPLE 24.

(a) *2 - Acetyl - 17β - acetoxyandrostan - 3-one.*

A mixture of 9.6 g. (0.16 mole) of glacial acetic acid and 50 ml. of ethylene dichloride was cooled in an ice-bath, and dry boron trifluoride gas was passed into the solution until it was saturated. With continued addition of boron trifluoride, a solution of 11.60 g. (0.04 mole) of androstan - 17β - ol-3 - one and 12,2 g. (11.4 ml., 0.12 mole) of acetic anhydride in 75 ml. of ethylene dichloride was added. The reaction mixture was stirred in the ice-bath for thirty minutes and at room temperature for three hours, and then poured into a solution of 30 g. of sodium acetate trihydrate in 200 ml. of water. The organic solvent was distilled off, and the residue refluxed for forty-five minutes and diluted with water. The solid product was collected by filtration, suspended in 200 ml. of methanol containing 23 ml. of 35% sodium hydroxide solution with stirring, 25 ml. of water was added, and the solution allowed to stand for one hour. The solution was acidified with glacial acetic acid, the methanol removed *in vacuo,* and water was added to precipitate a gummy product. The latter was separated, dried and dissolved in 25 ml. of acetic anhydride and 20 ml. of pyridine. The solution was kept at room temperature overnight and then heated for one hour on a steam bath. The reaction mixture was added to cold, dilute sulfuric acid and the product collected, washed, dissolved in hot methanol, and the solution filtered. Water was added to the filtrate to the point of turbidity, and the product which separated upon cooling was collected and dried at 70° C.; yield 11.59 g. m.p. 132—158° C. (uncorr.). The latter was dissolved in n-hexane and chromatographed on alumina. The fraction eluated with 20% ether in n-pentane was recrystallized from acetone and dried *in vacuo* at 110° C. for eight hours, giving 6.98 g. of 2 - acetyl - 17β - acetoxyandrostan - 3-one, m.p. 183.0—184.6° C. (corr.), $[\alpha]_D^{25} = +39.4 \pm 0.2°$ (1% in chloroform); ultraviolet maximum at 290 mμ (E = 9,100).

Anal. Calcd. for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15.
Found: C, 73.80; H, 9.55.

There was isolated from the foregoing reaction mixture as a byproduct, 2 - acetyl-3,17β - diacetoxy - 2 - androsten, the enol acetate of 2 - acetyl - 17β - acetoxyandrostan-3 - one, obtained in the form of colorless needles, m.p. 169.6—177.4° C. (corr.), $[\alpha]_D^{25} = +59.2 \pm 0.2°$ (1% in chloroform); ultraviolet maximum at 240 mμ (E = 8,850).

Anal. Calcd. for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71.
Found: C, 72.15; H, 8.63.

(b) *17β - Acetoxyandrostano [3.2-c] - 5¹-methylpyrazole* [VI; R is CH_3, R^1 is H, R^{11} is H, X is H_2, Z is $OCOCH_3$, Y and Y^1 are CH_3] was prepared from 3.00 g. of 2-acetyl-17β - acetoxyandrostan - 3 - one and 0.45 g. of hydrazine hydrate in 50 ml. of ethanol according to the manipulative procedure described above in Example 5. The resulting product was recrystallized from ethyl acetate and from aqueous ethanol and dried in vacuo for eight hours at 120—125° C., giving 17β - acetoxyandrostano [3.2-c] - 5¹-methylpyrazole, m.p. 254.0—262.8° C. (corr.), $[\alpha]_D^{25} = +41.7°$ (1% in chloroform); ultraviolet maximum at 224 mμ (E = 5,300).

Anal. Calcd. for $C_{23}H_{34}N_2O_2$: C, 74.55; H, 9.25; O, 8.64.
Found: C, 74.25; H, 9.06; O, 8.90.

17β - Acetoxyandrostano [3.2-c] - 5¹-methylpyrazole was saponified to give 17β-hydroxyandrostano [3.2-c] - 5¹ - methylpyrazole, m.p. 236.4—240.6° C. (corr.), $[\alpha]_D^{25} = +60.1°$ (1% in chloroform); ultraviolet maximum at 225 mμ (E = 5,400).

Anal. Calcd. for $C_{21}H_{32}N_2O$: C, 76.78; H, 9.82; N, 8.5.
Found: C, 76.84; H, 9.52; N, 8.4.

EXAMPLE 25.

(a) *2 - (n - Butyryl)androstan - 17β - ol - 3-one* was prepared by following the procedure of Example 24(a); m.p. 130.8—132.8° C. (corr.), colorless prisms from methanol, $[\alpha]_D^{25} = +55.8 \pm 0.1°$ (1% in chloroform); ultraviolet maximum at 290 mμ (E = 9,470).

(b) *17β - Hydroxyandrostano [3.2-c] - 5¹-(n-propyl)pyrazole* [VI; R is $(CH_2)_2CH_3$, R^1 and R^{11} are H, X is H_2, Z is OH, Y and Y^1 are CH_3] was then prepared by following the procedure of Example 5; m.p. 169.4—172.0° C. (corr.), needles from ethyl acetate, $[\alpha]_D^{25} = +56.5 \pm 0.2°$ (1% in chloroform); ultraviolet maximum at 224 mμ (E = 5,800).

EXAMPLE 26.

(a) *2 - Hydroxymethylene - 4,4 - dimethyl-5 - androsten - 17β - ol - 3 - one* was prepared by following the procedure of Example 16(a) and used to prepare

(b) *4,4 - Dimethyl - 17β - hydroxy - 5-androsteno [3.2-c] pyrazole* by following the procedure of Example 5; m.p. 231.0—233.6° C. (corr.), $[\alpha]_D^{25} = -20.1 \pm 0.4°$ (1% in chloroform); ultraviolet maximum at 224 mμ (E = 5,500).

Anal. Calcd. for $C_{22}H_{32}ON_2$: C,77.60; H, 9.47; N, 8.20.
Found: C, 78.17; H, 9.69; N, 8.40.

EXAMPLE 27.

(a) *2 - Hydroxymethylene - 4,4,17α - trimethylandrostan - 17β - ol - 3 - one* was prepared by following the procedure of Example 16(a); m.p. 150—154° C. (uncorr.).

(b) *4,4,17α - Trimethyl - 17β - hydroxyandrostano [3.2-c] - pyrazole* was then prepared by following the procedure of Example 5; m.p. 269.2—274.6° C. (corr.) when recrystallized from methanol; $[\alpha]_D^{25} = +4.7 \pm 0.1°$ (1% in 95% ethanol); ultraviolet maximum at 223 mμ (E = 4,930).

EXAMPLE 28.

(a) *2 - Hydroxmethylene - 6α,17α - dimethyl-4 - androsten - 17β - ol - 3 - one* was prepared by following the procedure of Example 2 and used to prepare

(b) *6α,17α - Dimethyl - 17β - hydroxy - 4-androsteno [3.2-c] - pyrazole* by following the procedure of Example 5; m.p. 170.0—178.6° C. (dec.) (corr.); ultraviolet maximum at 262 mμ (E = 9,200).

EXAMPLE 29.

(a) *Allopregnan - 3β - ol - 20 - one - ethylene glycol ketal.*

A mixture of 27.4 g. (0.086 mole of allopregnan - 3β - ol - 20 - one, 33 ml. of ethylene glycol, 700 ml. of benzene and 1 g. of *p*-toluenesulfonic acid was refluxed for seventy-eight hours with a water separator in the system. The reaction mixture was then cooled and shaken with 100 ml. of 2*N* sodium hydroxide solution, and the resulting mixture was filtered to collect 20.5 g. of allopregnan-3β - ol - 20 - one 20 - ethylene glycol ketal, m.p. 166—169° C. (uncorr.). When the latter was recrystallized from acetone, the compound was obtained in the form of colorless plates, m.p. 172.5—175° C. (uncorr.).

(b) *Allopregnane - 3,20 - dione 20 -ethylene glycol ketal.*

Chromic oxide (26.6 g.) was added in small portions to 425 ml. of pyridine at 25—30° C. To this mixture was added all at once a solution of 19.5 g. (0.054 mole) of allopregnan-3β - ol - 20 - one 20 - ethylene glycol ketal in 250 ml. of pyridine. The reaction mixture was stirred at room temperature for eighteen hours, diluted with 1 liter of hot benzene and filtered. The filtered solid was washed with 500 ml. of hot benzene, and the combined filtrates were washed with four 500 ml. portions of water followed by one 200 ml. portion of saturated sodium chloride solution. The organic solvent was then concentrated *in vacuo*, and the residue was triturated with 50 ml. of methanol. Filtration of the mixture and concentration of the filtrate to a volume of 20 ml. gave a small additional amount of solid product. The combined solid product was recrystallized from ethyl acetate using activated charcoal for decolorizing purposes to give 12.6 g. of allopregnane - 3,20 - dione 20 - ethylene glycol ketal in the form of blades and plates, m.p. 190—191.5° C. (uncorr.).

(c) *2 - Hydroxymethyleneallopregnane - 3,20-dione 20 - ethylene glycol ketal* was prepared from 2.45 g. of allopregnane - 3,20 - dione 20-ethylene glycol ketal, 20 ml. of ethyl formate,

and sodium methoxide (from 0.33 g. of sodium and 15 ml. of methanol) in 70 ml. of pyridine according to the manipulative procedure described above in Example 16, part (a). There was thus obtained 2.64 g. of 2 - hydroxymethyleneallopregnane - 3,20 - dione ~~20 - dione~~ 20 - ethylene glycol ketal, used in the next reaction without further purification.

A solution of 2.5 g. of 2 - hydroxymethyleneallopregnane - 3,20 - dione 20 - ethylene glycol ketal and 2 ml. of 2*N* hydrochloric acid in 50 ml. of ethanol was warmed at 50° C. for fifteen minutes and heated to boiling for two minutes. The solution was then concentrated and the residue recrystallized from a methylene chloride - ether - pentane (1:1:2) mixture and finally from a methylene chloride-pentane mixture to give 2 - hydroxymethyleneallopregnane - 3,20 - dione, m.p. 198.6—203.2° C. (corr.), $[\alpha]_D^{25} = +137.2 \pm 0.1°$ (1% in chloroform).

Anal. Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36.
Found: C, 76.41; H, 9.23.

(d) *20 - Oxoallopregnano [3.2-c] pyrazole 20 - ethylene glycol ketal* was prepared from 2.56 g. of 2 - hydroxymethylene allopregnane-3,20 - dione 20 - ethylene glycol ketal and 0.50 g. of hydrazine hydrate in 20 ml. of ethanol according to the manipulative procedure described above in Example 5. There was thus obtained 2.1 g. of 20 - oxoallopregnano [3.2-c] - pyrazole 20 - ethylene glycol ketal.

(e) *20 - Oxoallopregnano [3.2-c] pyrazole* [VI; R and R^1 are H, R^{11} is $COCH_3$, X is H_2, Z is H, Y and Y^1 are CH_3].

The 20 - oxoallopregnano [3.2-c] pyrazole 20 - ethylene glycol ketal obtained in part (d) above was suspended in 60 ml. of ethanol and 3 ml. of 2*N* hydrochloric acid was added with stirring. After the solid had dissolved (about two minutes), 4 ml. of water was added and the solution allowed to stand for twenty minutes. The solution was then made basic with dilute ammonium hydroxide and 125 ml. of water was added. The solid product was collected by filtration and recrystallized twice from ethanol to give 1.4 g. of 20 - oxoallopregnano [3.2-c] pyrazole in the form of colorless blades, m.p. 250—263.8° C. (corr.), $[\alpha]_D^{25} = +135.9 \pm 0.1°$ (1% in chloroform).

Anal. Calcd. for $C_{22}H_{32}N_2O$: C, 77.60; H, 9.47; N, 8.23.
Found: C, 77.94; H, 9.44; N, 8.16.

EXAMPLE 30.

17α,21 - Dihydroxy - 11,20 - dioxo - 4 - pregneno [3.2-c] pyrazole [VII; R and R^1 are H, R^{11} is $COCH_2OH$, X is O, Z is OH, Y and Y^1 are CH_3].

(a) *Without protection of the 20 - oxo group.*

21 - Acetoxy - 4 - pregnen - 17α - ol-3,11,20 - trione (cortisone acetate) (2.0 g., 0.005 mole) and 1.0 g. of sodium hydride in 100 ml. of pyridine were caused to react according to the manipulative procedure described above in Example 16, part (a), all operations being carried out in a nitrogen atmosphere. In the process the 21 - acetoxy group was saponified to give 1.3 g. of 2-hydroxymethylene - 4 - pregnene - 17α,21-diol - 3,11,20 - trione; ultraviolet maxima at 246 and 293 mμ (E = 8,000 and 4,300, respectively), characteristic of the 2 - hydroxymethylene - Δ^4 - 3 - oxo grouping.

2 - Hydroxymethylene - 4 - pregnene-17α,21 - diol - 3,11,20 - trione (1.3 g.) and 0.2 g. of hydrazine hydrate in 100 ml. of methanol were caused to react according to the manipulative procedure described above in Example 5. There was thus obtained 0.7 g. of 17α,21 - dihydroxy - 11,20 - dioxo - 4 - pregneno [3.2-c] pyrazole, m.p. above 320° C.; ultraviolet maximum at 260 mμ. The compound gave a positive Tollens test and triphenyltetrazolium test, characteristic of the ketol side chain.

(b) *By protection of the 20 - oxo group as the 17,20;20,21 - bis - methylenedioxy derivative.*

1. *2 - Hydroxymethylene - 4 - pregnene-17α,21 - diol - 3,11,20 - trione 17,20;20,21-bismethylenedioxy derivative* was prepared from 10.0 g. of 4 - pregnene - 17α,21 - diol-3,11,20 - trione 17,20;20,21 - bismethylenedioxy derivative, 15 ml. of ethyl formate and 1.3 g. of sodium hydride according to the manipulative procedure described above in Example 2. There was thus obtained 8.9 g. of 2 - hydroxymethylene - 4 - pregnene-17α,21 - diol - 3,11,20 - trione 17,20;20,21-bismethylenedioxy derivative; ultraviolet maxima at 252 and 309 mμ (E = 9,700 and 5,500, respectively). This material was used directly in the following reaction.

2. *17α,21 - Dihydroxy - 11,20 - dioxo - 4-pregneno - [3.2-c] pyrazole 17,20;20,21-bismethylenedioxy derivative* was prepared from 9.6 g. 2 - hydroxymethylene - 4 - pregnene - 17α,21 - diol - 3,11,20 - trione 17,20;20,21 - bismethylenedioxy derivative and 4.0 ml. of hydrazine hydrate in 250 ml. of ethanol according to the manipulative pro-

cedure described above in Example 5. There was thus obtained 8.2 g. of 17α,21 - dihydroxy-11,20 - dioxo - 4 - pregneno [3.2-c] pyrazole 17,20;20,21 - bismethylenedioxy derivative, m.p. above 300° C. (corr.) when recrystallized from dimethylformamide.

Anal. Calcd. for $C_{24}H_{30}N_2O_5$: C, 67.37; H, 6.88; O, 19.10.
Found: C, 67.58; H, 7.09; O, 18.76.

3. *17α,21 - Dihydroxy - 11,20 - dioxo - 4-pregnano - [3.2-c] pyrazole* was prepared by heating 17α,21 - dihydroxy - 11,20 - dioxo-4 - pregneno - [3.2-c] pyrazole 17,20;20,21-bis-methylenedioxy derivative with dilute formic acid. The product had properties similar to those of the product obtained in part (a) above.

EXAMPLE 31.

(a) *20 - Oxoallopregnano [3.2-c] - 1¹-methylpyrazole* [VI; R is H, R¹ is CH_3, R¹¹ is $COCH_3$, X is H_2, Z is H, Y and Y¹ are CH_3] was prepared by reacting the product of Example 29(c) with methyl hydrazine followed by hydrolysis of the ketal with ethanolic hydrochloric acid as in Example 29(e); m.p. 194—211° C. (uncorr.), $[\alpha]_D^{25} = +126.0 \pm 0.2°$ (1% in chloroform); ultraviolet maximum at 232 mμ (E = 6,507).

Anal. Calcd. for $C_{23}H_{34}N_2O$: C, 77.92; H, 9.67; N, 7.90.
Found: C, 78.10; H, 9.69; N, 7.81.

(b) There was prepared the methiodide salt of 20 - oxoallopregnano [3.2-c] - 1¹ - methylpyrazole from the product of Example 31(a) and methyl iodide in the form of yellow needles, m.p. 277.6—295.8° C. (dec.) (corr.), $[\alpha]_D^{25} = +97.1 \pm 0.1°$ (0.5% in methanol).

EXAMPLE 32.

17α - Methyl - 17β - hydroxyandrostano [3.2-c] - 2¹ - methylpyrazole [VI; R is H, R¹ and R¹¹ are CH_3, X is H_2, Z is OH, Y and Y¹ are CH_3].

A mixture of 8.52 g. of 2 - hydroxymethylene - 17α - methylandrostan - 17β - ol - 3-one and 2.31 g. of methylsemicarbazide [$H_2NCON(CH_3)NH_2$] was heated in *n*-butyl alcohol solution on a steam bath for four hours. There was then added 5 ml. of water, and the mixture was refluxed for eighteen hours and concentrated *in vacuo*. The residue was dissolved in methylene dichloride, and the solution was washed with water, dried with sodium sulfate and concentrated to dryness. The residue was triturated with ether, and the resulting crystalline product was heated in a nitrogen atmosphere for six hours at 205° C. to effect cyclization. The resulting product was dissolved in benzene and chromatographed on a column of alumina. The column was eluted with benzene containing increasing amounts of ether. The crystalline product was isolated from eluants containing 20% ether and recrystallized from acetone to give 17α - methyl - 17β - hydroxyandrostano [3.2-c] - 2¹ - methylpyrazole, m.p. 186.6—198.0° C. (corr.), $[\alpha]_D^{25} = +38.3°$ (1% in ethanol); ultraviolet maxima at 229 and 270 mμ (E = 4,932 and 100, respectively).

Anal. Calcd. for $C_{20}H_{34}N_2O$: C, 77.14; H, 10.01; N, 8.18.
Found: C, 77.24; H, 10.17; N, 8.09.

EXAMPLE 33.

17β - Propionoxyandrostano [3.2-c] - N-propionylpyrazole [VI; R is H, R¹ is CH_3CH_2CO, R¹¹ is H, X is H_2, Z is OH, Y and Y¹ are CH_3] was prepared by esterification of the product of Example 6(b) with propionic anhydride; m.p. 178—181° C. (uncorr.) after two recrystallizations from ether.

17β - Acetoxy - 17α - methylandrostano [3.2-c] - N - acetylpyrazole was obtained by refluxing for thirty minutes a mixture of 2.05 g. of 17β - hydroxyandrostano [3.2-c] pyrazole with 20.0 ml. of acetic anhydride. The product had an ultraviolet maximum at 258 mμ (E = 12,500).

EXAMPLE 34.

(a) *2 - Hydroxymethylene - 17α - methyletiocholan - 17β - ol - 3 - one.*

To 4.8 g. (0.2 mole) of sodium hydride suspended in 75 ml. of benzene was added 3.2 g. (0.1 mole) of methanol. After the reaction subsided, the mixture was heated to boiling, cooled, and treated with a mixture of 20.8 g. (0.068 mole) of 17α - methyletiocholan - 17β-ol - 3 - one, 75 ml. of benzene, and 21 ml. of ethyl formate. The mixture was stirred vigorously for four hours, mixed with 200 ml. of water, and the layers were separated. The water layer was washed with ether and then acidified with hydrochloric acid. The result-

ing precipitate was collected by filtration and dried, giving 17.8 g. of 2 - hydroxymethylene-17α - methyletiocholan - 17β - ol - 3 - one, suitable for use in the succeeding reaction. A sample was further purified by chromatography on 100 g. of silica gel in an equal volume of mixture of ether and pentane. The resulting solid was recrystallized from ether, giving colorless needles, m.p. 205.6—211.6° C. (corr.), $[\alpha]_D^{25} = +0.3 \pm 0.2°$ (1% in chloroform); ultraviolet maxima at 285 and 347 mμ (E = 7,200 and 1.500, respectively).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70.
Found: C, 75.69; H, 9.74.

(b) *17β - Hydroxy - 17α - methyletiocholano [3.2-c] pyrazole* [VI; R and R^1 are H, R^{11} is CH_3, X is H_2, Z is OH, Y and Y^1 are CH_3] was prepared from 2.0 g. of 2 - hydroxymethylene - 17α - methyletiocholan - 17β-ol - 3 - one and 2 g. of hydrazine hydrate in 25 ml. of ethanol according to the manipulative procedure described above in Example 5. The product was recrystallized from ethyl acetate to give 17β - hydroxy - 17α - methyletiocholano [3.2-c] pyrazole in the form of colorless leaflets, m.p. 271.4—279.6° C. (corr.), $[\alpha]_D^{25} = -23 \pm 4°$ (1.19% in chloroform).

Anal. Calcd. for $C_{21}H_{32}N_2O$: C, 76.78; H, 9.82; N, 8.53.
Found: C, 76.76; H, 9.87; N, 8.73.

A solution of 2.0 g. of 17β - hydroxy - 17α-methyl - 4 - androsteno [3.2-c] pyrazole in 200 ml. of glacial acetic acid was hydrogenated in the presence of 1.0 g. of platinum oxide catalyst. The catalyst was then removed by filtration and the filtrate concentrated *in vacuo*. The residue was dissolved in 100 ml. of methanol, made basic with concentrated ammonium hydroxide and again concentrated *in vacuo*. This residue was crystallized from ethyl acetate to give 0.7 g. of product, m.p. 260—265° C. (uncorr.), undepressed upon admixture with a sample of 17β - hydroxy-17α - methyltiocholano [3.2-c] pyrazole prepared as described above. The ultraviolet and infrared spectra of the samples prepared by the two alternative methods were identical. This proved that the hydroxymethylene group had entered the 2 - position of the 17α-methyletiocholan - 17β - ol - 3 - one in part (a) above.

EXAMPLE 35.

(a) *6α,17α - Dimethylandrostan - 17β - ol - 3-one.*

A solution of 10.0 g. of 6α,17α - dimethyl-4 - androsten - 17β-ol - 3 - one in 150 ml. of ether and 150 ml. of tetrahydrofuran was added to 1 liter of anhydrous liquid ammonia. Lithium (2.5 g.) was added in small pieces and the mixture was stirred for fifty minutes. There was then added 20 g. of solid ammonium chloride in small portions, the ammonia was evaporated on a steam bath, 2.5 liters of water was added and the mixture stirred for one hour. The solid product which had separated was collected by filtration and dried, giving 9.89 g., m.p. 145—200° C. (uncorr.). The latter product was dissolved in an ether-methylene dichloridepentane (30:10:60) mixture and chromatographed on 500 g. of silica gel. The chromatographed product was recrystallized from ethyl acetate to give 6α,17α -dimethylandrostan - 17β - ol - 3-one in the form of colorless prismatic crystals, m.p. 181.6—184.6° C. (corr.), $[\alpha]_D^{25} = +10.3 \pm 0.2°$ (1% in chloroform).

(b) *2 - Hydroxymethylene - 6α,17α - dimethylandrostan - 17β - ol - 3 - one* was prepared according to Example 1(a) from the product of Example 35(a) above; m.p. 198—199.8° C. (corr.) when recrystallized from acetone; $[\alpha]_D^{25} = +54.3 \pm 0.1°$ (1% in chloroform); ultraviolet maximum at 285 mμ (E = 9,200).

Anal. Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89.
Found: C, 75.93; H, 9.63.

(c) *6α,17α - Dimethyl - 17β - hydroxyandrostano [3.2-c] pyrazole* was prepared by following the procedure of Example 5; m.p. 156.0—174.0° C. (dec.) (corr.), $[\alpha]_D^{25} = +44.8 \pm 0.1°$ (1% in chloroform); ultraviolet maximum at 225 mμ (E = 4,900).

EXAMPLE 36.

(a) *2 - Hydroxymethylene - 17α - vinylandrostan - 17β - ol - 3 - one* was prepared by following the procedure of Example 2 and used to prepare

(b) *17β - Hydroxy - 17α - vinylandrostano [3.2-c] pyrazole* [VI; R and R^1 are H, R^{11} is $CH=CH_2$, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. above 300° C. (corr.), $[\alpha]_D^{25} = +24.5 \pm 0.8°$ (1% in chloroform); ultraviolet maximum at 224 mμ (E = 7,100).

Anal. Calcd. for $C_{22}H_{32}N_2O$: C, 77.60; H, 9.47; N, 8.23; O, 4.70.
Found: C, 77.52; H, 9.70; N, 8.00; O, 4.50.

EXAMPLE 37.

(a) *2 - Hydroxymethylene - 17α - ethyl - 19-norandrostan - 17β - ol - 3 - one* was prepared by following the procedure of Example 2; m.p. 77—115° C. (uncorr.), used directly in the following reaction without further purification.

(b) *17α - Ethyl - 17β - hydroxy - 19 - norandrostano [3.2-c] pyrazole* [VI; R and R^1 are H, R^{11} is C_2H_5, X is H_2, Z is OH, Y is H, Y^1 is CH_3] was prepared by following the procedure of Example 5; m.p. 149.2—150.4° C. (corr.), $[\alpha]_D^{25} = +93.0 \pm 0.1°$ (1% in pyridine).

EXAMPLE 38.

(a) *2 - Hydroxymethylenepregnane - 3,20-dione* was prepared by following the procedure of Example 16(a); m.p. 139.8—146.0° C. when recrystallized from methanol, $[\alpha]_D^{25} = +114.2 \pm 0.3°$ (1% in chloroform).

(b) *20 - Oxopregnano [3.2-c] pyrazole* [VI; R and R^1 are H, R^1 is COCH, X is H_2, Z is H, Y and Y^1 are CH_3 was prepared by following the procedure of Example 5; m.p. 231.2—253.0° C. (corr.), $[\alpha]_D^{25} = +91.6 \pm 0.1°$ (1% in chloroform).

EXAMPLE 39.

(a) *2 - Hydroxymethylene - 17α - ethynyl-androstan - 17β - ol - 3 - one* was prepared by following the procedure of Example 16(a) and used to prepare

(b) *17α - Ethynyl - 17α - hydroxyandrostano [3.2-c] pyrazole* [VI; R and R^1 are H, R^{11} is C≡CH, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. 237.4—242.0° C. (corr.), $[\alpha]_D^{25} = +12.4 \pm 0.1°$ (1% in chloroform); ultraviolet maximum at 223 mμ (E = 5,100).

Anal. Calcd. for $C_{22}H_{30}N_2O$: C, 78.06; H, 8.93; N, 8.28.
Found: C, 77.87; H, 9.20; N, 8.37.

EXAMPLE 40.

(a) *2 - Hydroxymethylene - 17α - allyl - 4-androsten - 17β - ol - 3 - one* was prepared by following the procedure of Example 16(a) and used to prepare

(b) *17α - Allyl - 17β - hydroxy - 4 - androsteno [3.2-c] pyrazole* [VII; R and R^1 are H, R^{11} is $CH_2CH=CH$, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. 239.8—248.2° C. (corr.), $[\alpha]_D^{25} = +93.7 \pm 0.1°$ (1% in chloroform); ultraviolet maximum at 260 mμ (E = 10,500).

EXAMPLE 41.

(a) *5α,6α - Epoxy - 17α - propynylandrostane-3β,17β - diol 3 - acetate.*

A mixture of 2.82 g. of 17α - propynyl - 5-androstene - 3β,17β - diol 3 - acetate [m.p. 195.4—201.2° C. (corr.), $[\alpha]_D^{25} = -117.8 \pm 0.1°$ (1% in chloroform), prepared from 5-androsten - 3β - ol - 17 - one and propynylmagnesium bromide, followed by acetylation with acetic anhydride in pyridine], 13.5 ml. of peracetic acid and 2.00 g. of sodium acetate trihydrate in 200 ml. of chloroform was allowed to react at room temperature for about two days. The reaction mixture was then washed successively with 250 ml. of water, 250 ml. of 5% sodium carbonate solution, 250 ml. of 1*N* sodium hydroxide solution and 250 ml. of water. The washings were back extracted with ether, and the ether was successively washed with 100 ml. of water, 100 ml. of 1*N* sodium hydroxide solution, 100 ml. of water and 100 ml. of sodium chloride solution. The combined organic solutions were dried and concentrated, and the residue was dissolved in pentane containing 10% ether and chromatographed on silica gel. The chromatographed product was recrystallized from ethyl acetate to give 5α,6α - epoxy - 17α-propynylandrostane - 3β,17β - diol 3 - acetate in the form of colorless prisms, m.p. 244.6—250.6° C. (corr.), $[\alpha]_D^{25} = -111.3 \pm 0.1°$ (1% in chloroform).

Anal. Calcd. for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87.
Found: C, 74.74; H, 8.95.

(b) *6β - Methyl - 17α - propynylandrostane-3β,5α,17β - triol.*

Methylmagnesium iodide was prepared from 36.28 g. of magnesium and 215.4 g. of methyl iodide in 625 ml. of ether. The ether was gradually removed by distillation and replaced with benzene. A solution of 34.13 g. of *5α,6α*-epoxy - 17α - propynylandrostane - 3β,17β-diol 3 - acetate in 2500 ml. of benzene was then added, and the mixture was refluxed for two and one-half hours. Saturated ammonium chloride solution (250 ml.) was added, the mixture was filtered and the benzene solution concentrated. The residue was extracted with ethyl acetate and the total organic product isolated, giving about 20 g. of 6β - methyl - 17α-propynylandrostane - 3β,5α,17β - triol in the form of colorless rods, m.p. 212—213.5° C. (uncorr.) when recrystallized from ethyl acetate.

(c) *6β - Methyl - 17α - propynylandrostane-5α,17β - diol - 3 - one.*

A mixture of 18.2 mg. of 6β - methyl - 17α-propynylandrostane - 3β,5α,17β - triol and 18.2 g. of chromic oxide in 360 ml. of pyridine was stirred for twenty-four hours at room temperature. The reaction mixture was worked up by extraction with ethyl acetate and washing with acid to remove pyridine. There was thus obtained 7.24 g. of 6β - methyl - 17α-propynylandrostane - 5α,17β - diol - 3 - one, m.p. 249.2—256.2° C. (corr.) when recrystallized from ethyl acetate; $[\alpha]_D^{25} = -43.7$ (1% in chloroform).

Anal. Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56.
Found: C, 77.20; H, 9.34.

(d) *6α - Methyl - 17α - propynyl - 4 - androsten - 17β - ol - 3 - one.*

A solution of 10.72 g. of 6β - methyl - 17α-propynylandrostane - 5α,17β - diol - 3 - one and 5.00 g. of potassium hydroxide in 400 ml. of methanol and 40 ml. of water was refluxed for two hours under a nitrogen atmosphere. The reaction mixture was cooled, 5 ml. of acetic acid was added and the solution concentrated *in vacuo*. The residue was extracted with ethyl acetate, and the ethyl acetate solution was washed with ammonium carbonate solution, water and sodium chloride solution, dried and concentrated to give 5.51 g. of product, m.p. 85—101° C. (uncorr.). The latter product was chromatographed on silica gel and recrystallized from aqueous ethanol to give 6α - methyl - 17α - propynyl - 4-androsten - 17β - ol - 3 - one in the form of colorless plates, m.p. 90—110° C. (uncorr.).

(e) *2 - Hydroxymethylene - 6α - methyl - 17α-propynyl - 4 - androsten - 17β - ol - 3 - one* was prepared by following the procedure of Example 2; m.p. 89—93° C. (uncorr.).

(f) *17β - Hydroxy - 6α - methyl - 17α-propynyl - 4 - androsteno [3.2-c] pyrazole* was prepared by following the procedure of Example 5; m.p. indefinite starting at 160.4° C. (corr.), $[\alpha]_D^{25} = +3.6 \pm 0.9°$ (1% in chloroform).

EXAMPLE 42.

(a) *2 - Hydroxymethylene - 17α - ethyl - 4,6-androstadien - 17β - ol - 3 - one* was prepared by following the procedure of Example 2; and used to prepare

(b) *17β - Hydroxy - 17α - ethyl - 4,6 - androstadieno [3.2-c] pyrazole* [VIII; R and R^1 are H, R^{11} is C_2H_5, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. above 300° C. (corr.), $[\alpha]_D^{25} = -55.4 \pm 0.1°$ (1% in pyridine); ultraviolet maxima at 220, 225, 232, 288, 297 and 308 mμ (E = 7,500, 8,500, 7,700, 8,400, 21,800 and 16,400, respectively).

EXAMPLE 43.

17β - Hydroxy - 17α - methylandrostano [3.2-c] - N - (4 - chlorophenoxyacetyl)-pyrazole [VI; R is H, R^1 is 4-$ClC_6H_4OCH_2CO$, R^{11} is CH_3, X is H_2, Z is OH, Y and Y^1 are CH_3] was prepared from the product of Example 1(b) and 4 - chlorophenoxyacetic anhydride in pyridine; m.p. 164.8—167.6° C. (corr.), $[\alpha]_D^{25} = +35 \pm 0.2°$ (1% in chloroform); ultraviolet maxima at 228, 260 and 287 mμ (E = 14,000, 18,300 and 1,700, respectively).

EXAMPLE 44.

17β - Hydroxy - 17α - methyl - 4 - androsteno [3.2-c] - N - acetylpyrazole [VII; R is H, R^1 is $COCH_3$, R^{11} is CH_3, X is H_2, Z is OH, Y and Y^1 are CH_3] was prepared from the product of Example 13(b) and acetic anhydride in pyridine: m.p. 92.0—100.2° C. (corr.), $[\alpha]_D^{25} = +67.1 \pm 0.2°$ (1% in chloroform); ultraviolet maxima at 237, 256 and 289 mμ (E = 7,400, 6,300 and 22,100, respectively). The analytical sample was dried at 125° C. *in vacuo* over phosphorus pentoxide.

EXAMPLE 45.

17β - Hydroxy - 17α - methylandrostano [3.2-c] - N - propionyl pyrazole [VI; R is H, R^1 is $COCH_2CH_3$, R^{11} is CH_3, X is H_2, Z is OH, Y and Y^1 are CH_3] was prepared from the product of Example 1(b) and propionic anhydride in pyridine; m.p. indefinite starting at 121.8°

C. (corr.), $[\alpha]_D^{25} = +43.5°$ (1% in chloroform); ultraviolet maximum at 258 mμ (E = 18,800).

EXAMPLE 46.

(a) *17α - Propyl - 4 - androsten - 17β - ol - 3 - one* was prepared by Oppenhauer oxidation of 17α - propyl - 5 - androsten - 3β,17β-diol; m.p. 114.6—116.0° C. (1% in chloroform); ultraviolet maximum at 241 mμ (E = 16,800).

(b) *2 - Hydroxymethylene - 17α - propyl - 4-androsten - 17β - ol - 3 - one* was prepared by following the procedure of Example 2 and used to prepare

(c) *17β - Hydroxy - 17α - propyl - 4 - androsteno [3.2-c] pyrazole* [VII; R and R^1 are H, R^{11} is $CH_2CH_2CH_3$, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. 223.0—233.4° C. (corr.), $[\alpha]_D^{25} = +89.5°$ (1% in chloroform); ultraviolet maximum at 260 mμ (E = 9,816).

EXAMPLE 47.

(a) *2 - Hydroxymethylene - 17α - propargyl-4 - androsten - 17β - ol - 3 - one* was prepared by following the procedure of Example 2 and used to prepare

(b) *17β - Hydroxy - 17α - propargyl - 4-androsteno [3.2-c] pyrazole* [VII; R and R^1 are H, R^{11} is $CH_2C{\equiv}CH$, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. 130.4—140.6° C. (corr.), $[\alpha]_D^{25} = +75.4°$ (1% in chloroform); ultraviolet maximum at 261 mμ (E = 9,714).

EXAMPLE 48.

17β - Hydroxy - 17α - methyl - 4 - androsteno [3.2-c] - 1' - methylpyrazole [VII; R is H, R^1 and R^{11} are CH_3, X is H_2, Z is OH, Y and Y^1 are CH_3] was prepared by following the procedure of Example 4; m.p. 175.2—193.2° C. (corr.), $[\alpha]_D^{25} = +103.6°$ (1% in chloroform); ultraviolet maximum at 272 mμ (E = 10,400).

EXAMPLE 49.

17β - Hydroxy - 17α - methyl - 4 - androsteno [3.2-c] - 1' - methylpyrazole methiodide was prepared from the product of Example 48 and methyl iodide; m.p. 257.8—261.6° C. (dec.) (corr.), $[\alpha]_D^{25} = +13.3°$ (0.5% in methanol).

EXAMPLE 50.

(a) *2 - Hydroxymethylene - 19 - norandrostan - 17β - ol - 3 -one* was prepared by following the procedure of Example 16(a) and used to prepare

(b) *17β - Hydroxy - 19 - norandrostano [3.2-c] pyrazole* [VI; R, R^1 and R^{11} are H, X is H_2, Z is OH, Y is H, Y^1 is CH_3] by following the procedure of Example 5; m.p. indefinite starting at 141.6° C. (corr.).

EXAMPLE 51.

(a) *2 - Hydroxymethylene - 17α - propyl-androstan - 17β - ol - 3 - one* was prepared by following the procedure of Example 2 and used to prepare

(b) *17β - Hydroxy - 17α - propylandrostano [3.2-c] pyrazole* [VI; R and R^1 are H, R^{11} is $CH_2CH_2CH_3$, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. 217.6—220.8° C. (corr.), $[\alpha]_D^{25} = +35.2°$ (1% in chloroform); ultraviolet maximum at 224 mμ (E = 4,800).

EXAMPLE 52.

(a) *2 - Hydroxymethylene - 4 - pregnene-11β,17α,21 - triol - 3,20 - dione 17,20;20,21-bismethylenedioxy derivative* was prepared by following the procedure of Example 2 and used to prepare

(b) *11β,17α,21 - Trihydroxy - 20 - oxo - 4-pregneno [3.2-c] pyrazole 17,20;20,21 - bismethylenedioxy derivative* by following the procedure of Example 5; m.p. 210—240° C. (uncorr.). Chromatography on silica gel and recrystallization from an ethanol-ethyl acetate mixture gave a sample having the m.p. 301—304° C. (uncorr.).

EXAMPLE 53.

(a) *2 - Hydroxymethylene - 9 - fluoro - 4-pregnene - 11β,17α,21 - triol - 3,20 - dione 17,20;20,21 - bismethylenedioxy derivative* was prepared by following the procedure of Example 2; m.p. 150—170° C.

(b) *9α - Fluoro - 11β,17α,21 - trihydroxy - 20-oxo - 4 - pregneno - [3.2-c] pyrazole 17,20; 20,21 - bismethylenedioxy derivative* was prepared by following the procedure of Example 5; m.p. 220—260° C. (uncorr.).

EXAMPLE 54.

(a) *2 - Hydroxymethylene - 4 - androstene-11β,17β - diol - 3 - one* was prepared by following the procedure of Example 2; m.p. 168—190° C. (uncorr.); ultraviolet maxima at 251 and 307 mμ (E = 11,700 and 5,200, respectively).

(b) *11β,17β - Dihydroxy - 4 - androsteno [3.2-c] pyrazole* [VII; R, R^1 and R^{11} are H, X is (H)(OH), Z is OH, Y and Y^1 are CH_3] was prepared by following the procedure of Example 5; m.p. 233.2—246.0° C. (corr.); ultraviolet maximum at 262 mμ (E = 10,700).

EXAMPLE 55.

(a) *2 - Hydroxymethylene - 17α - methyl-19 - nor - 4 - androsten - 17β - ol - 3 - one* was prepared by following the procedure of Example 2; ultraviolet maximum at 246 mμ (E = 10,800).

(b) *17α - Methyl - 17β - hydroxy - 19 - nor-4 - androsteno [3.2-c] - pyrazole* [VII; R and R^1 are H, R^{11} is CH_3, X is H_2, Z is OH, Y is H, Y^1 is CH_3] was prepared by following the procedure of Example 5; m.p. 111.0—126° C. (dec.) (corr.), $[\alpha]_D^{25} = +0.2°$ (1% in chloroform).

EXAMPLE 56.

(a) *2-Hydroxymethylene - 17α-propynylandrostan - 17β - ol - 3 - one* was prepared by following the procedure of Example 1(a) and used to prepare

(b) *17β - Hydroxy - 17α - propylandrostano [3.2-c] - pyrazole* [VI; R and R^1 are H, R^{11} is $C{\equiv}CCH_3$, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. indefinite starting at 143.2° C. (corr.), $[\alpha]_D^{25} = -29.6°$ (1% in pyridine), $-29.3°$ (1% in dimethylformamide); ultraviolet maximum at 224 mμ (E = 5,400).

EXAMPLE 57.

5α,6α - Epoxy - 17β - hydroxy - 17α - methylandrostano [3.2-c] pyrazole.

A solution of 2.00 g. of 17β - hydroxy - 17α - methyl - 4 - androsteno [3.2-c] pyrazole and 21.21 ml. of an ethereal solution of 0.302*M* monoperphthalic acid in 979 ml. of ethyl acetate was allowed to react at room temperature for ninety-three hours. The product was isolated and recrystallized from an ethyl acetate-methanol mixture to give 1.37 g. of 5α,6α-epoxy - 17β - hydroxy - 17α - methylandrostano [3,2-c] pyrazole, m.p. 253—258° C. (uncorr.). A further recrystallization from methanol gave a sample having the m.p. 259.5—264° C. (uncorr.), partially solidifying and remelting above 300° C.; ultraviolet maximum at 238 mμ (E = 18,300).

WHAT WE CLAIM IS:—

1. A process for preparing a pyrazole compound fused through its 3- and 4-positions to the 3- and 2-positions, respectively, of a steroid nucleus, said steroid having from eighteen to twenty-three carbon atoms exclusive of ester radicals, or acid addition or quaternary ammonium salts thereof, which comprises reacting the required 2 - (1 - hydroxyalkylidene)-3 - oxo - steroid with a hydrazine or a hydrazine mono-substituted by a radical inert under the conditions of the reaction, if desired, reacting the pyrazole compound obtained from the reaction with unsubstituted hydrazine with a carboxylic acid anhydride or with cyanic acid, and, if desired, obtaining acid addition or quaternary ammonium salts of the basic compounds obtained.

2. A process according to claim 1, in which the compound prepared has the formula (VI herein), wherein R is hydrogen or a lower-alkyl radical; R^1 is hydrogen, a lower alkyl radical, a monocarbocyclic aryl, a lower-alkanoyl, the carbamyl or the guanyl radical; R^{11} is hydrogen, a lower-alkyl, a lower-alkenyl, a lower-alkynyl, the acetyl, a ketalized acetyl, a hydroxyacetyl, a ketalized hydroxyacetyl, the 1,2 - dihydroxyethyl or the 1 - hydroxyethyl radical; X is H_2, (H) (OH) or O; Y and Y^1 are hydrogen or the methyl radical; and Z is hydrogen or the hydroxy radical, Z being restricted to hydroxy when R^{11} is hydrogen, a lower-alkynyl, the acetyl, a ketalized acetyl, alkynyl radical; or a carboxylic acid ester derived from a carboxylic acid having from one to ten carbon atoms and having a molecular weight less than 250 of said compound, if desired, said compound having one double bond in the 4,5 - position (Formula VII) or having two double bonds, one in the 4,5 - position and the other in the 6,7-position (Formula VIII); and the steroid has the formula (IX herein) wherein R, R^{11}, X, Z and Y and Y^1 and the location of any double bonds in the steroid nucleus are identical with their selection above, and the hydrazine has the formula R^1NHNH_2 wherein R^1 is identical with its selection above.

3. A process according to claim 1, in which 17β - hydroxy - 17α - methylandrostano [3.2-c]pyrazole is prepared by reacting 2-hydroxymethylene - 17α - methylandrostan-17β - ol - 3 - one with hydrazine.

4. A process for preparing a pyrazole compound fused through its 3- and 4-positions to the 3- and 2-positions, respectively, of a steroid nucleus, said steroid having from eighteen to twenty-three carbon atoms exclusive of ester radicals, or acid addition or quaternary ammonium salts thereof, substantially as herein described with reference to the Examples.

5. Compounds prepared by the process according to any one of the preceding claims.

6. A steroido [3.2-c]pyrazole, said steroid moiety having from eighteen to twenty-three carbon atoms exclusive of ester radicals.

7. Steroids having the formula (VI herein) wherein R is hydrogen or a lower-alkyl radical; R^1 is hydrogen, a lower-alkyl, a monocarbocyclic aryl, a lower-alkanoyl, a monocarbocyclic aryloxy - lower - alkanoyl, the carbamyl, or the guanyl radical; R^{11} is hydrogen, a lower-alkyl radical, a lower-alkenyl radical, a lower-alkynyl radical, the acetyl radical, a ketalized cetyl, the hydroxyacetyl, a ketalized hydroxyacetyl, the 1,2 - dihydroxyethyl or the 1-hydroxyethyl radical; X is H_2, (H) (OH) or O; Y and Y^1 are hydrogen or the methyl radical; and Z is hydrogen or the hydroxy radical, Z being restricted to hydroxy when R^{11} is hydrogen, a lower-alkyl, a lower-alkenyl or a lower-alkynyl radical; or carboxylic acid esters of said steroids derived from carboxylic acids having from one to ten carbon atoms and having a molecular weight less than 250.

8. Steroids having the formula (VII herein) wherein R is hydrogen or a lower-alkyl radical; R^1 is hydrogen, a lower-alkyl, a monocarbocyclic aryl, a lower-alkanoyl, monocarbocyclic aryloxy-lower-alkanoyl, the carbamyl, or the guanyl radical; R^{11} is hydrogen, a lower-alkyl

(b) *17α - Methyl - 17β - hydroxy - 19 - nor-4 - androsteno [3.2-c] - pyrazole* [VII; R and R^1 are H, R^{11} is CH_3, X is H_2, Z is OH, Y is H, Y^1 is CH_3] was prepared by following the procedure of Example 5; m.p. 111.0—126° C. (dec.) (corr.), $[\alpha]_D^{25} = +0.2°$ (1% in chloroform).

EXAMPLE 56.

(a) *2-Hydroxymethylene - 17α-propynylandrostan - 17β - ol - 3 - one* was prepared by following the procedure of Example 1(a) and used to prepare

(b) *17β - Hydroxy - 17α - propylandrostano [3.2-c] - pyrazole* [VI; R and R^1 are H, R^{11} is $C{\equiv}CCH_3$, X is H_2, Z is OH, Y and Y^1 are CH_3] by following the procedure of Example 5; m.p. indefinite starting at 143.2° C. (corr.), $[\alpha]_D^{25} = -29.6°$ (1% in pyridine), $-29.3°$ (1% in dimethylformamide); ultraviolet maximum at 224 mμ (E = 5,400).

EXAMPLE 57.

5α,6α - Epoxy - 17β - hydroxy - 17α - methylandrostano [3.2-c] pyrazole.

A solution of 2.00 g. of 17β - hydroxy - 17α - methyl - 4 - androsteno [3.2-c] pyrazole and 21.21 ml. of an ethereal solution of 0.302*M* monoperphthalic acid in 979 ml. of ethyl acetate was allowed to react at room temperature for ninety-three hours. The product was isolated and recrystallized from an ethyl acetate-methanol mixture to give 1.37 g. of 5α,6α-epoxy - 17β - hydroxy - 17α - methylandrostano [3,2-c] pyrazole, m.p. 253—258° C. (uncorr.). A further recrystallization from methanol gave a sample having the m.p. 259.5—264° C. (uncorr.), partially solidifying and remelting above 300° C.; ultraviolet maximum at 238 mμ (E = 18,300).

WHAT WE CLAIM IS:—

1. A process for preparing a pyrazole compound fused through its 3- and 4-positions to the 3- and 2-positions, respectively, of a steroid nucleus, said steroid having from eighteen to twenty-three carbon atoms exclusive of ester radicals, or acid addition or quaternary ammonium salts thereof, which comprises reacting the required 2 - (1 - hydroxyalkylidene)-3 - oxo - steroid with a hydrazine or a hydrazine mono-substituted by a radical inert under the conditions of the reaction, if desired, reacting the pyrazole compound obtained from the reaction with unsubstituted hydrazine with a carboxylic acid anhydride or with cyanic acid, and, if desired, obtaining acid addition or quaternary ammonium salts of the basic compounds obtained.

2. A process according to claim 1, in which the compound prepared has the formula (VI herein), wherein R is hydrogen or a lower-alkyl radical; R^1 is hydrogen, a lower alkyl radical, a monocarbocyclic aryl, a lower-alkanoyl, the carbamyl or the guanyl radical; R^{11} is hydrogen, a lower-alkyl, a lower-alkenyl, a lower-alkynyl, the acetyl, a ketalized acetyl, a hydroxyacetyl, a ketalized hydroxyacetyl, the 1,2 - dihydroxyethyl or the 1 - hydroxyethyl radical; X is H_2, (H) (OH) or O; Y and Y^1 are hydrogen or the methyl radical; and Z is hydrogen or the hydroxy radical, Z being restricted to hydroxy when R^{11} is hydrogen, a lower-alkynyl, the acetyl, a ketalized acetyl, alkynyl radical; or a carboxylic acid ester derived from a carboxylic acid having from one to ten carbon atoms and having a molecular weight less than 250 of said compound, if desired, said compound having one double bond in the 4,5 - position (Formula VII) or having two double bonds, one in the 4,5 - position and the other in the 6,7-position (Formula VIII); and the steroid has the formula (IX herein) wherein R, R^{11}, X, Z and Y and Y^1 and the location of any double bonds in the steroid nucleus are identical with their selection above, and the hydrazine has the formula R^1NHNH_2 wherein R^1 is identical with its selection above.

3. A process according to claim 1, in which 17β - hydroxy - 17α - methylandrostano [3.2-c]pyrazole is prepared by reacting 2-hydroxymethylene - 17α - methylandrostan-17β - ol - 3 - one with hydrazine.

4. A process for preparing a pyrazole compound fused through its 3- and 4-positions to the 3- and 2-positions, respectively, of a steroid nucleus, said steroid having from eighteen to twenty-three carbon atoms exclusive of ester radicals, or acid addition or quaternary ammonium salts thereof, substantially as herein described with reference to the Examples.

5. Compounds prepared by the process according to any one of the preceding claims.

6. A steroido [3.2-c]pyrazole, said steroid moiety having from eighteen to twenty-three carbon atoms exclusive of ester radicals.

7. Steroids having the formula (VI herein) wherein R is hydrogen or a lower-alkyl radical; R^1 is hydrogen, a lower-alkyl, a monocarbocyclic aryl, a lower-alkanoyl, a monocarbocyclic aryloxy - lower - alkanoyl, the carbamyl, or the guanyl radical; R^{11} is hydrogen, a lower-alkyl radical, a lower-alkenyl radical, a lower-alkynyl radical, the acetyl radical, a ketalized acetyl, the hydroxyacetyl, a ketalized hydroxyacetyl, the 1,2 - dihydroxyethyl or the 1-hydroxyethyl radical; X is H_2, (H) (OH) or O; Y and Y^1 are hydrogen or the methyl radical; and Z is hydrogen or the hydroxy radical, Z being restricted to hydroxy when R^{11} is hydrogen, a lower-alkyl, a lower-alkenyl or a lower-alkynyl radical; or carboxylic acid esters of said steroids derived from carboxylic acids having from one to ten carbon atoms and having a molecular weight less than 250.

8. Steroids having the formula (VII herein) wherein R is hydrogen or a lower-alkyl radical; R^1 is hydrogen, a lower-alkyl, a monocarbocyclic aryl, a lower-alkanoyl, monocarbocyclic aryloxy-lower-alkanoyl, the carbamyl, or the guanyl radical; R^{11} is hydrogen, a lower-alkyl

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radical, a lower-alkenyl radical, a lower-alkynyl radical, the acetyl radical, a ketalized acetyl, the hydroxyacetyl, a ketalized hydroxyacetyl, the 1,2 - dihydroxyethyl or the 1-hydroxyethyl radical; X is H_2, (H) (OH) or O; Y and Y^1 are hydrogen or the methyl radical; and Z is hydrogen or the hydroxy radical, Z being restricted to hydroxy when R^{11} is hydrogen, a lower-alkyl, a lower-alkenyl or a lower-alkynyl radical; or carboxylic acid esters of said steroids derived from carboxylic acids having from one to ten carbon atoms and having a molecular weight less than 250.

9. Steroids having the formula (VIII herein) wherein R is hydrogen or a lower-alkyl radical; R^1 is hydrogen, a lower-alkyl, a monocarbocyclic aryl, a lower-alkanoyl, monocarbocyclic aryloxy - lower - alkanoyl, the carbamyl, or the guanyl radical; R^{11} is hydrogen, a lower-alkyl radical, a lower-alkenyl radical, a lower-alkynyl radical, the acetyl radical, a ketalized acetyl, the hydroxyacetyl, a ketalized hydroxyacetyl, the 1,2 - dihydroxyethyl or the 1 - hydroxyethyl radical; X is H_2, (H) (OH) or O; Y and Y^1 are hydrogen or the methyl radical; and Z is hydrogen or the hydroxy radical, Z being restricted to hydroxy when R^{11} is hydrogen, a lower-alkyl, a lower-alkenyl or a lower-alkynyl radical; or carboxylic acid esters of said steroids derived from carboxylic acids having from one to ten carbon atoms and having a molecular weight less than 250.

10. 17β - Hydroxy - 17α - methylandrostano[3.2-c]pyrazole.

11. 17β - Hydroxy - 17α - methylandrostano[3.2-c] - N - acetylpyrazole.

12. 17β - Hydroxy - 17α - methylandrostano[3.2-c] - 1^1 - methylpyrazole.

13. 17β - Hydroxy - 17α - methylandrostano[3.2-c] - N - phenylpyrazole.

14. 17β - Hydroxyandrostano[3.2-c]-pyrazole.

15. 17β - Propionoxyandrostano[3.2-c]-pyrazole.

16. 17β - Hydroxy - 17α - ethylandrostano-[3.2-c]pyrazole.

17. 17β - Hydroxy - 17α - methyl - 19-norandrostano[3.2-c]pyrazole.

18. 17β - Acetoxyandrostano[3.2-c] - 5^1-methylpyrazole.

19. 17β - Hydroxyandrostano[3.2-c] - 5^1-(n - propyl)pyrazole.

20. 20 - Oxoallopregnano[3.2-c]pyrazole.

21. 20 - Oxoallopregnano[3.2-c] - 1^1-methylpyrazole.

22. 17β - Hydroxy - 17α-methyletiocholano-[3.2-c]pyrazole.

23. 17β - Hydroxy - 17α - vinylandrostano[3.2-c]pyrazole.

24. 17α - Ethyl - 17β - hydroxy - 19 - norandrostano[3.2-c]pyrazole.

25. 20 - Oxopregnano[3.2-c]pyrazole.

26. 17α - Ethynyl - 17β - hydroxyandrostano[3.2-c]pyrazole.

27. 17β - Hydroxy - 17α - methylandrostano[3.2-c] - N - (4 - chlorophenoxyacetyl)-pyrazole.

28. 17β - Hydroxy - 17α - methylandrostano[3.2-c] - N - propionylpyrazole.

29. 17β - Hydroxy - 19 - norandrostano-[3.2-c]pyrazole.

30. 17β - Hydroxy - 17α - propylandrostano[3.2-c]pyrazole.

31. 17β - Hydroxy - 17α - propynylandrostano[3.2-c]pyrazole.

32. 17β - Hydroxy - 4 - androsteno[3.2-c]-pyrazole - N - carboxamide.

33. 17β - Hydroxy - 17α - methyl - 4-androsteno[3.2-c]pyrazole.

34. 17β - Hydroxy - 4 - androsteno[3.2-c]-pyrazole.

35. 17β - Hydroxy - 17α - ethyl - 4 - androsteno[3.2-c]pyrazole.

36. 17β - Hydroxy - 17α - vinyl - 4 - androsteno[3.2-c]pyrazole.

37. 17α - Ethynyl - 17β - hydroxy - 4-androsteno[3.2-c]pyrazole.

38. 20β - Hydroxy - 4 - pregneno[3.2-c]-pyrazole.

39. 20β - Hydroxy - 4 - pregneno[3.2-c]-pyrazole - N - carboxamide.

40. 20 - Oxo - 4 - pregneno[3.2-c]pyrazole-N - carboxamide.

41. 20 - Oxo - 4 - pregneno[3.2-c]-pyrazole.

42. 17α,21 - Dihydroxy - 11,20 - dioxo-4 - pregneno[3.2-c]pyrazole.

43. 17α - Allyl - 17β - hydroxy - 4 - androsteno[3.2-c]pyrazole.

44. 17β - Hydroxy - 17α - methyl - 4-androsteno[3.2-c] - N - acetylpyrazole.

45. 17β - Hydroxy - 17α - propyl - 4-androsteno[3.2-c]pyrazole.

46. 17β - Hydroxy - 17α - propargyl - 4-androsteno[3.2-c]pyrazole.

47. 17β - Hydroxy - 17α - methyl - 4-androsteno[3.2-c] - 1^1 - methylpyrazole.

48. 17β - Hydroxy - 17α - methyl - 4,6-androstadieno[3.2-c]pyrazole.

49. 17β - Hydroxy - 4,6 - androstadieno-[3.2-c]pyrazole.

50. 17β - Hydroxy - 17α - ethyl - 4,6-androstadieno[3.2-c]pyrazole.

51. 17 - Oxo - 4 - androsteno[3.2-c]-pyrazole.

52. 17β - Hydroxy - 4,4,17α - trimethyl-5 - androsteno[3.2-c]pyrazole.

53. 4,4 - Dimethyl - 17β - hydroxy - 5-androsteno[3.2-c]pyrazole.

54. 4,4,17α - Trimethyl - 17β - hydroxy-androstano[3.2-c]pyrazole.

55. 6α,17α - Dimethyl - 17β - hydroxy - 4-androsteno[3.2-c] - pyrazole.

56. 6α,17α - Dimethyl - 17β - hydroxy-androstano[3.2-c]pyrazole.

57. 17β - Hydroxy - 6α - methyl - 17α-propynyl - 4 - androsteno[3.2-c]pyrazole.

58. Acid addition or quaternary ammonium salts of the basic members of the compounds

* C L M S *

according to any one of claims 6—57.

59. A compound according to claim 58, in which the quaternary ammonium salt is the methiodide.

60. A compound according to claim 6 as herein described with reference to the Examples.

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