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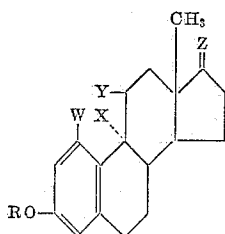
3,076,829

NOVEL 9,11-DISUBSTITUTED ESTRADIENE DERIVATIVES

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This invention is concerned with novel, therapeutically active 9,11-disubstituted estrogens and methods for their manufacture. More specifically, this invention relates to novel 9 α ,11 β -disubstituted-1,3,5(10)-estratrienes and analogs thereof, which possess estrogenic activity.

Included among the novel estratrienes of our invention are compounds having the following structural formula:



wherein W is a member of the group consisting of H and methyl; R is a member of the group consisting of H, lower alkyl, and an acid radical of an acid of the group consisting of sulfuric acid and carboxylic acids having up to 8 carbon atoms; X is a halogen having an atomic weight less than 100; Y is a member of the group consisting of keto,



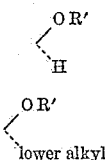
and



R' being a member of the group consisting of H and lower alkanoyl, X' being a halogen having an atomic weight less than 40 and when Y is



X must have an atomic weight greater than 20; and Z is a member of the group consisting of keto,



and



wherein R' is as heretofore defined.

By "lower alkyl" is meant a hydrocarbon radical having up to 4 carbon atoms such as methyl, ethyl, propyl, isopropyl, butyl, sec-butyl and tert-butyl.

Illustrative of the carboxylic acid esters contemplated are lower alkanooates such as acetate, propionate, butyrate, valerate, caproate, and t-butyl-acetate; aroyl esters such as benzoate and toluate, and esters from dibasic organic acids such as succinate, phthalate and sulfobenzoate. Also included in the term "acid radical"

2

are the alkali metal salts of the dibasic carboxylic acid esters such as, for example, the 3,17-di-sodium hemisuccinate of 9 α -chloro-11-ketoestradiol.

The above definition of the novel compounds of our invention should not be strictly construed but rather may be considered to admit the presence of other substituents on the steroid nucleus, particularly at positions 6 and 16, such as 6 α -methyl, 6 α -fluoro, 6 α -chloro, 16 α -hydroxy, 16 α -acyloxy, 16-methyl and 16-halogen analogs thereof. This modification depends solely on the choice of starting material employed, which in the instant case would involve the employment of a 9(11)-dehydroestratriene starting steroid possessing the desired substituent in the positions indicated, which substituents are introduced by methods known in the art.

The novel estratrienes defined by the general formula possess estrogenic activity and thus are therapeutically useful in the treatment of the menopausal syndrome, in female hypogonadism, functional uterine bleeding, and post partum breast engorgement. The novel 9,11-disubstituted estratrienes are also useful for the lowering of blood cholesterol, and may also be used in cosmetics for topical application. Our novel estrogens may be administered parenterally in aqueous or oil suspension for intra-muscular injection or in pellet form for subcutaneous implantation; and orally in tablet form. Our novel 9,11-disubstituted estrogens may be used in the usual dosage forms and in the same manner as other known estrogens such as Estinyl (17 α -ethinylestradiol) and Progynon (estradiol).

Among the 9,11-disubstituted-estratrienes of our invention are 9 α ,11 β -dihalogeno derivatives such as 9 α ,11 β -dichloroestrone (i.e., 9 α ,11 β -dichloro-1,3,5(10)-estratriene-3-ol-17-one) and the 3-acetate and 3-benzoate esters thereof, 9 α ,11 β -dichloro-17 α -ethinylestradiol 3-benzoate (i.e., 9 α ,11 β -dichloro-17 α -ethinyl-1,3,5(10)-estratriene-3,17 β -diol 3-benzoate), 9 α -chloro-11 β -fluoroestradiol diacetate, 9 α -bromo-11 β -fluoroestrone 3-methyl ether, 1,17 α -dimethyl-9 α ,11 β -dichloroestradiol 3-methyl ether, 1-methyl-9 α -fluoro-11 β -chloroestrone 3-methyl ether; 9 α -halogeno-11-keto derivatives such as 9 α -bromo-11-ketoestrone, 9 α -chloro-11-ketoestradiol, 9 α -fluoro-11-ketoestrone - acetate, 1-methyl - 9 α -bromo-11 - keto-17 α -ethinyl estradiol 3-methyl ether and the 17-acetate thereof; and 9 α ,11 β -halohydrins and esters thereof such as 9 α -bromo-11 β -hydroxyestrone 3-acetate, 9 α -chloro-11 β -hydroxyestradiol 3,17-diacetate, 9 α -chloro-11 β -formyloxyestradiol 3,17-diacetate, 1-methyl-9 α -fluoro-11 β -hydroxy-17 α -ethinylestradiol 3-acetate and 1,17 α -dimethyl-9 α -bromo-11 β -hydroxyestradiol 3-methyl ether.

Of the novel, therapeutically active estratrienes of our invention the 1-desmethylestratrienes are preferred over the 1-methylestratrienes and, of the 1-desmethylestratrienes, the 9 α ,11 β -dihalogeno- and 9 α -fluoro-11 β -hydroxy derivatives are particularly valuable, such as, for example, 9 α ,11 β -dichloroestrone, 9 α -chloro-11 β -fluoroestrone, 9 α ,11 β -dichloro-17 α -ethinylestradiol, 9 α -chloro-11 β -fluoro-17 α -ethinylestradiol, and esters thereof and 9 α -fluoro-11 β -hydroxyestrone.

The novel 9,11-disubstituted-estratrienes of our invention are prepared from the corresponding 1,3,5(10),9(11)-estratetraene derivatives by the addition of halogen, hypohalous acid, or halogen acylate to the 9(11)-double bond, utilizing techniques analogous to those known in the art. Some 1,3,5(10),9(11)-estratetraene starting compounds are known, such as 9(11)-dehydroestrone, the 3-methyl ether, 3-acetate ester, and derivatives thereof, as well as 9(11)-dehydroestradiol and its 3-methyl ether. Other 9(11)-dehydro starting compounds such as 17 α -methyl-9(11)-dehydroestradiol and 17 α -ethinyl-9(11)-dehydroestradiol are readily prepared from 9(11)-dehy-

droestrone by known methods. For example, 9(11)-dehydroestrone is readily transformed to 17 α -methyl-9(11)-dehydroestradiol by the well known Grignard reagent methyl magnesium iodide. By utilizing other lower alkyl Grignard reagents such as ethyl magnesium bromide, 9(11)-dehydroestrone may be converted to other 17 α -lower alkyl derivatives, e.g., 17 α -ethyl-9(11)-dehydroestradiol. Similarly, 9(11)-dehydroestrone may be transformed to 17 α -ethynylestradiol by means of sodium or potassium acetylide. Those 9(11)-dehydroestrone and 9(11)-dehydroestradiol starting compounds having a 1-methyl substituent are prepared as described in copending application of Reimann, Serial No. 138,270, filed on even date with the instant application. By this method, a steroidal 3-keto-1,4,9(11)-triene of the pregnane or androstane series is heated with a strong acid catalyst (e.g., p-toluene-sulfonic acid or trifluoroacetic anhydride) in an acid solvent, preferably a lower alkanolic acid or anhydride (e.g., acetic acid, or acetic anhydride) whereby the 3-keto-1,4-dehydro-A-ring is aromatized to give the corresponding 1-methyl-3-hydroxy-1,3,5(10)-estratriene. For example, when 1,4,9(11)-androstatriene-3,17-dione in acetic acid in the presence of p-toluenesulfonic acid is heated on the steam bath there is formed 1-methyl-9(11)-dehydroestrone (1-methyl-1,3,5(10),9(11)-estratetraene-3-ol-17-one).

In the manufacture of our novel 9,11-disubstituted estratriene derivatives, the additions to the 9(11)-double bond of the starting 1,3,5(10),9(11)-estratetraenes are carried out according to procedures similar to those described in the literature. Thus, when preparing the 9 α ,11 β -dihalogeno estratrienes of our invention, i.e., the 9 α ,11 β -dichloro-, 9 α -bromo-11 β -chloro-, 9 α -bromo-11 β -fluoro-, and 9 α -chloro-11 β -fluoro-derivatives, there is utilized a halogen or halogen donor such as N-bromoacetamide, chlorine, or N-chlorosuccinimide in the presence of a halide anion such as chloride or fluoride according to procedures similar to those described in U.S. Patent No. 2,894,963 and in J. Org. Chem. 26, 866 (1961). Thus, for example, when 9(11)-dehydroestrone 3-methyl ether in carbon tetrachloride is reacted with chlorine in the presence of pyridine there is obtained 9 α ,11 β -dichloroestrone 3-methyl ether; whereas when hydrogen fluoride and N-chlorosuccinimide are the reagents utilized, the compound 9 α -chloro-11 β -fluoroestrone 3-methyl ether is produced. Similarly, when 9(11)-dehydroestradiol diacetate in diethylacetic acid is reacted with N-bromoacetamide and hydrogen fluoride, 9 α -bromo-11 β -fluoroestradiol diacetate is formed, whereas reaction with lithium chloride/N-bromoacetamide/anhydrous hydrogen chloride gives 9 α -bromo-11 β -chloroestradiol diacetate. When preparing 9,11-dihalogenoestratriene derivatives, it is preferable to have any primary or secondary hydroxyl groups protected prior to halogenation (such as by preparing an ester, e.g., an acetate by reaction with acetic anhydride and pyridine). Thus, for example, 1,17 α -dimethyl-9(11)-dehydroestradiol is converted to the corresponding 3-acetate ester by reaction with acetic anhydride in pyridine prior to halogenation with hydrogen fluoride and N-chlorosuccinimide. The resultant product, 1,17 α -dimethyl-9 α -chloro-11 β -fluoroestradiol 3-acetate, may then be hydrolyzed to the 3-ol by conventional methods such as with methanolic potassium carbonate.

The novel 9 α -halogeno-11-alkanoyloxy-1,3,5(10)-estratrienes of our invention are derived from the corresponding 9(11)-dehydroestrogens by reaction with a halogen donor such as N-bromoacetamide or N-chlorosuccinimide in the presence of a source of acylate such as formic, acetic, propionic acids or the like according to procedures similar to those described by Robinson et al. J. Am. Chem. Soc. 81, 2195 (1959). Thus, for example, 9(11)-dehydroestradiol diacetate when reacted with N-bromoacetamide and lithium acetate in glacial acetic acid yields the corresponding 9 α -bromo-11 β -acetoxy derivative, i.e., 9 α -bromo-11 β -acetoxyestradiol diacetate. Similarly,

9(11)-dehydroestradiol diacetate upon reaction with formic acid containing sodium formate and N-chlorosuccinimide with one equivalent of anhydrous hydrogen chloride is converted to 9 α -chloro-11 β -formyloxyestradiol diacetate. The 9 α -fluoro-11 β -acyloxy derivatives are most conveniently obtained by esterification of the corresponding 11-hydroxy derivatives such as by heating with the desired acid in the presence of trifluoroacetic anhydride. For example, 9 α -fluoro-11 β -hydroxyestrone 3-acetate heated with glacial acetic acid and trifluoroacetic anhydride is converted to 9 α -fluoro-11 β -acetoxyestrone 3-acetate.

Introduction of the 9 α -halogeno-11 β -hydroxy groups into the 9(11)-dehydroestratriene starting compounds of our process may be accomplished by the use of a halogen donor such as N-bromosuccinimide in the presence of water and a strong acid such as perchloric acid. Thus 9(11)-dehydroestrone 3-acetate reacted with N-bromosuccinimide and perchloric acid yields a novel estratriene of our invention, namely 9 α -bromo-11 β -hydroxyestrone 3-acetate. Other 9 α -halogeno derivatives are obtained from the corresponding bromohydrin such as the aforementioned, by refluxing with mild alkali, e.g., potassium acetate in acetone, to form the corresponding 9 β ,11 β -oxido derivatives, e.g., 9 β ,11 β -oxidoestrone 3-acetate. The oxido intermediates are then reacted with hydrogen fluoride in chloroform with or without ethanol and/or tetrahydrofuran to form fluorohydrins, e.g., 9 α -fluoro-11 β -hydroxyestrone 3-acetate. Similarly, the substitution of anhydrous hydrogen chloride for hydrogen fluoride in this reaction results in the production of the corresponding 9 α -chloro derivatives, e.g., 9 α -chloro-11 β -hydroxyestrone 3-acetate.

The novel 9 α -halogeno-11-keto-estratrienes of our invention are conveniently derived by oxidation of the corresponding 11-hydroxy derivative using an oxidizing agent such as chromic acid. Thus, 1-methyl-9 α -bromo-11 β -hydroxyestradiol 3,17-diacetate upon oxidation with chromic acid yields an 11-keto compound of our invention, namely, 1-methyl-9 α -bromo-11-keto-estradiol 3,17-diacetate. Alternatively, 9 α -bromo-11 β -hydroxyestrone, 9 α -bromo-11-ketoestrone and 9 β ,11 β -oxidoestrone may be prepared from the corresponding 19-nor-4-androstene-3-one by microbiological 1,2-dehydrogenation, for example, with *Corynebacterium simplex*.

In the preparation of our novel 9,11-disubstituted estrogens, it is preferable to carry out all desired modifications of the molecule prior to addition to the 9(11)-double bond. Thus, it is preferable, for example, to convert 9(11)-dehydroestrone by means of ethyl magnesium bromide to 17 α -ethyl-9(11)-dehydroestradiol followed by esterification at the 3-position by means of acetic anhydride in pyridine prior to halogenation, for example, with chlorine in carbon tetrachloride to give the novel compound of this invention, 9 α ,11 β -dichloro-17 α -ethyl-estradiol 3-acetate. It is to be noted that the primary and secondary hydroxyl groups are preferentially protected such as by ester groups during all the addition reactions. When preparing the 17 α -ethynyl analogs, however, it is usually preferable to carry out the ethination reaction after the substituents have been introduced at C-9 and C-11. For example, 9 α -chloro-11 β -fluoroestrone 3-methyl ether of our invention is converted to another novel estratriene by reaction with sodium acetylide to give 9 α -chloro-11 β -fluoro-17 α -ethynylestradiol 3-methyl ether.

The following are examples which illustrate our invention. It is to be understood that the invention is not to be limited to the exact details of operation or exact compounds shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art; the invention is therefore to be limited only by the scope of the appended claims.

EXAMPLE 1

9(11)-Dehydroestrone Acetate

To a solution of 1.0 g. of 9(11)-dehydroestrone in 5 ml. of pyridine is added 0.8 ml. of acetic anhydride. The mixture is allowed to stand at room temperature for 3 hours. It is then poured into ice water and the resulting precipitate is filtered, washed with water, dried, and crystallized from ethyl acetate-ether and ethyl acetate-pentane to give 9(11)-dehydroestrone acetate, M.P. 115–117° C.; $[\alpha]_D^{23} +234^\circ$ (CHCl_3);

$$\lambda_{\text{max}}^{\text{MeOH}} 257 \text{ m}\mu \ (\epsilon 17,100)$$

Similarly, by substituting other lower alkanic acid anhydrides, such as valeric and caprylic anhydrides, for acetic anhydride in the procedure of this example there is obtained 9(11)-dehydroestrone valerate and 9(11)-dehydroestrone caprylate, respectively.

EXAMPLE 2

9(11)-Dehydroestrone Benzoate

To a solution of 784 mg. of 9(11)-dehydroestrone in 10 ml. of pyridine is added 1 ml. of benzoyl chloride. The mixture is allowed to stand at room temperature overnight, and is then poured into ice-water, and stirred for 20 minutes. The resulting precipitate is filtered, washed, dried, and crystallized from acetone-hexane to give 9(11)-dehydroestrone benzoate, M.P. 232–234° C.; $[\alpha]_D^{23} +238^\circ$ (CHCl_3);

$$\lambda_{\text{max}}^{\text{MeOH}} 256 \text{ m}\mu \ (\epsilon 19,600)$$

Similarly by substituting other acid chlorides such as m-toluy chloride for benzoyl chloride in the procedure of this example there is obtained 9(11)-dehydroestrone m-toluate.

EXAMPLE 3

9 α ,11 β -Dichloroestrone Acetate

To a solution of 250 mg. of 9(11)-dehydroestrone acetate and 1.0 g. of lithium chloride in 12 ml. of acetic acid is added 114 mg. of 98% N-chlorosuccinimide and 0.25 ml. of a 7 N solution of hydrogen chloride in tetrahydrofuran. The mixture is allowed to stir in the dark for 20 minutes, then poured into ice water. The resulting precipitate is filtered, washed, dried and crystallized from methylene chloride-pentane to give 9 α ,11 β -dichloroestrone acetate, M.P. 161–169° C. dec.; $[\alpha]_D^{23} +13^\circ$ (CHCl_3).

EXAMPLE 4

9 α -Bromo-11 β -Hydroxyestrone Acetate

To a solution of 250 mg. of 9(11)-dehydroestrone acetate in 25 ml. of dioxane and 2.5 ml. of water is added 150 mg. of N-bromosuccinimide and 1 ml. of a 1.5 N solution of perchloric acid. The mixture is stirred in the dark for 3 hours, then poured into ice-water. A precipitate separates which is filtered, washed with water, dried and crystallized from methylene chloride-pentane to give 9 α -bromo-11 β -hydroxyestrone acetate.

Similarly, 9(11)-dehydroestrone valerate and 9(11)-dehydroestrone caprylate may be reacted according to the above procedure to give the valerate and caprylate esters, respectively, of 9 α -bromo-11 β -hydroxyestrone.

EXAMPLE 5

9 α -Bromo-11-Ketoestrone

A sample of 4.05 g. of 9 α -bromo-11-keto-19-nor-4-androstene-3,17-dione is subjected to the action of a culture of *Corynebacterium simplex* (ATCC 6946) in a manner similar to those given in U.S. Patent 2,837,464 as follows:

From a solution of 30 g. of yeast extract (Difco) in 3.0 l. of tap water containing 13.2 g. of potassium dihydrogen phosphate and 26.4 g. of disodium hydrogen phosphate (pH of the solution 6.9) 27 portions of 100

ml. each are withdrawn, placed in 300 ml. of Erlenmeyer flasks and sterilized by autoclaving for 15 minutes at 15 lb. steam pressure (120° C.). After autoclaving and cooling of the broth one ml. of a suspension of *Corynebacterium simplex* (ATCC 6946) is placed in each flask. The flasks are then shaken on a shake table at 220 r.p.m. and 28° C. for 24 hours.

In each of 27 Erlenmeyer flasks are placed 150 mg. of 9 α -bromo-11-keto-19-nor-4-androstene-3,17-dione. The flasks and contents are then sterilized for 15 minutes at 15 lb. steam pressure (120° C.). To each flask is then added 5.0 ml. of ethanol. The 24-hour bacterial culture is then transferred aseptically and the resulting suspensions are shaken on a shake table at 220 r.p.m. and 28° C. for 48 hours. The final pH is 7.2.

The contents of all the flasks are combined and extracted with a total of 9.0 l. of chloroform in three equal portions. The combined extracts are then concentrated to a residue which is crystallized from methylene chloride-pentane to give 9 α -bromo-11-ketoestrone.

EXAMPLE 6

9 α -Fluoro-11 β -Hydroxyestrone 3-Acetate and 9 α -Chloro-11 β -Hydroxyestrone 3-Acetate

A. 9 β ,11 β -oxidoestrone acetate.—To a solution of 150 mg. of 9 α -bromo-11 β -hydroxyestrone acetate in 10 ml. of acetone, is added 300 mg. of potassium acetate. The mixture is heated under reflux for 17 hours, then poured into ice-water. A precipitate separates which is filtered, washed with water, dried and crystallized from acetone-hexane to give 9 β ,11 β -oxidoestrone acetate. The Beilstein test done on a sample of this compound for the presence of halogen is negative.

In a similar manner, the valerate and caprylate esters of 9 α -bromo-11 β -hydroxyestrone are converted to 9 β ,11 β -oxidoestrone valerate and 9 β ,11 β -oxidoestrone caprylate, respectively.

Alternatively, the compound of this example is prepared by subjecting 500 mg. of 9 β ,11 β -oxido-19-nor-4-androstene-3,17-dione to the action of *Corynebacterium simplex* (ATCC 6946) in the manner of Example 5 yielding 9 β ,11 β -oxidoestrone which is acetylated with acetic anhydride in pyridine according to the procedure of Example 1.

B. 9 α -fluoro-11 β -hydroxyestrone 3-acetate.—A solution of 500 mg. of 9 β ,11 β -oxidoestrone acetate in 20 ml. of methylene chloride is cooled in an ice-bath and 2 ml. of 48% aqueous hydrofluoric acid is added with stirring. The mixture is vigorously stirred in the cold for 3 hours, then poured into cold aqueous sodium bicarbonate solution. The organic layer is separated, washed with water and concentrated in vacuo to a residue which is crystallized from acetone-hexane to give 9 α -fluoro-11 β -hydroxyestrone 3-acetate.

Similarly, the valerate and caprylate esters of 9 β ,11 β -oxidoestrone are converted to 9 α -fluoro-11 β -hydroxyestrone valerate and 9 α -fluoro-11 β -hydroxyestrone caprylate, respectively.

C. 9 α -chloro-11 β -hydroxyestrone 3-acetate.—To a solution of 100 mg. of 9 β ,11 β -oxidoestrone acetate in 10 ml. of chloroform is added anhydrous hydrogen chloride gas at –20° C. for 3 minutes. The reaction mixture is chilled for two hours, then extracted with aqueous sodium acetate. The organic solution is then concentrated in vacuo to a residue which is crystallized from methylene chloride-pentane to give 9 α -chloro-11 β -hydroxyestrone 3-acetate.

EXAMPLE 7

9 α -Fluoro-11 β -Acetoxyestrone 3-Acetate

A solution of 450 mg. of 9 α -fluoro-11 β -hydroxyestrone 3-acetate in 5 ml. of glacial acetic acid and 1 ml. of tri-fluoroacetic anhydride is heated on the steam bath for 30 minutes. The reaction mixture is then poured into ice-water and the resultant precipitate filtered, washed, dried,

7

and crystallized from acetone-hexane to give 9 α -fluoro-11 β -acetoxyestrone 3-acetate.

EXAMPLE 8

9 α -Fluoro-11-Ketoestrone Acetate

To a solution of 100 mg. of 9 α -fluoro-11 β -hydroxyestrone 3-acetate in 5 ml. of acetone is added 0.2 ml. of chromic acid-sulfuric acid reagent (266 mg. chromic acid/ml.). The mixture is left at room temperature for 2 hours, then the excess reagent is destroyed by the addition of a small amount of methanol and the solution is diluted with water. The resulting precipitate is filtered, washed, dried, and crystallized from acetone-hexane to give 9 α -fluoro-11-ketoestrone acetate.

EXAMPLE 9

9 α ,11 β -Dichloroestrone Benzoate

A solution of 500 mg. of 9(11)-dehydroestrone benzoate (the compound of Example 2) in 25 ml. of carbon tetrachloride and 0.4 ml. of pyridine is cooled to -20° C. and 0.78 ml. of a solution of chlorine in carbon tetrachloride (122 mg. Cl₂/ml.) is added. The mixture is stirred at -20° C. for 30 minutes, then allowed to warm to room temperature. Sufficient methylene chloride is added to give a clear solution which is then allowed to stand overnight. The solution is then concentrated in vacuo to a small volume. A precipitate separates which is filtered and crystallized from methylene chloride-pentane to give 9 α ,11 β -dichloroestrone benzoate M.P. 136–143° C. dec.; $[\alpha]_D^{+10.1}$ (dioxane).

Similarly, the m-toluate ester of 9(11)-dehydroestrone is reacted with chlorine in carbon tetrachloride to give 9 α ,11 β -dichloroestrone m-toluate.

EXAMPLE 10

17 α -Ethinyl-9 α ,11 β -Dichloroestradiol 3-Benzoate

1.5 ml. of 17% sodium acetylide in xylene is centrifuged, then the xylene is decanted and 2 ml. of dimethylsulfoxide added. The resultant suspension of sodium acetylide in dimethylsulfoxide is added to a solution of 250 mg. of 9 α ,11 β -dichloroestrone benzoate in 6 ml. of dimethylsulfoxide. The reaction mixture is stirred at 20° C. for 10 minutes, then poured into ice water. The resulting precipitate is filtered, washed, dried and chromatographed on silica gel. Fractions are eluted with hexane-ether mixtures and those fractions combined which do not show the 17-keto band in the infrared. Crystallization of these fractions from methylene chloride-pentane gives 17 α -ethinyl-9 α ,11 β -dichloroestradiol 3-benzoate.

EXAMPLE 11

9(11)-Dehydroestradiol Diacetate

A. 9(11)-dehydroestradiol.—To a solution of 3.0 g. of 9(11)-dehydroestrone in 300 ml. of methanol, chilled in ice, is added 1.0 g. of sodium borohydride. The solution is stirred at room temperature for 100 minutes, then is poured into ice-water and the solution acidified with acetic acid. The resulting precipitate is filtered, washed with water, and crystallized from acetone-hexane to give 9(11)-dehydroestradiol, M.P. 191–193° C.

B. 9(11)-dehydroestradiol diacetate.—A solution of 3.0 g. of 9(11)-dehydroestradiol in 25 ml. of pyridine and 3 ml. of acetic anhydride is allowed to stand at room temperature for 18 hours. The reaction mixture is then poured into ice-water. A solid separates, which is filtered, washed with water, dried, and crystallized from acetone-hexane to give 9(11)-dehydroestradiol diacetate, M.P. 152–153° C.; $[\alpha]_D^{+88.4}$ (dioxane);

$$\lambda_{\text{max}}^{\text{MeOH}} 258 \text{ m}\mu, \epsilon 17,400$$

By substituting other acid anhydrides such as caproic and propionic anhydrides for acetic anhydride in the above procedure, there is obtained the corresponding di-

8

acylate, i.e. the dicaproate and dipropionate, respectively, of 9(11)-dehydroestradiol.

EXAMPLE 12

9(11)-Dehydroestradiol Dibenzoate

To a solution of 800 mg. 9(11)-dehydroestradiol in 10 ml. of pyridine is added 1 ml. of benzoyl chloride. The mixture is kept at room temperature for 16 hours, then is poured into ice-water and stirred for 1 hour. The resulting precipitate is filtered and crystallized from methylene chloride-pentane to give 9(11)-dehydroestradiol dibenzoate, M.P. 185–187° C.

EXAMPLE 13

9 α -Bromo-11 β -Hydroxyestradiol 3,17-Diacetate

To a solution of 500 mg. of 9(11)-dehydroestradiol diacetate in 50 ml. of dioxane is added 210 mg. of N-bromoacetamide, 5.0 ml. of water and 2.0 ml. of 1.5 N perchloric acid. The mixture is stirred in the dark at room temperature for 2.5 hours, then poured into ice-water. A gummy precipitate separates which is dissolved in methylene chloride, and crystallized from methylene chloride-pentane to give 9 α -bromo-11 β -hydroxyestradiol 3,17-diacetate, M.P. 119–124° C. dec.

Similarly, the dicaproate and dipropionate esters of 9(11)-dehydroestrone may be reacted with N-bromoacetamide according to the above procedure to give 9 α -bromo-11 β -hydroxyestradiol 3,17-dicaproate and 9 α -bromo-11 β -hydroxyestradiol 3,17-dipropionate, respectively.

EXAMPLE 14

9 α -Fluoro-11 β -Hydroxyestradiol 3,17-Diacetate

A. 9 β , 11 β -oxidoestradiol diacetate.—9 α -bromo-11 β -hydroxyestradiol 3,17-diacetate (100 mg.) is treated with potassium acetate in acetone according to the procedure of Example 6A. The resultant product is crystallized from acetone-hexane to give 9 β ,11 β -oxidoestradiol diacetate, M.P. 122–124° C.

B. 9 α -fluoro-11 β -hydroxyestradiol 3,17-diacetate.—A sample of 200 mg. of 9 β ,11 β -oxidoestradiol diacetate is allowed to react with hydrofluoric acid according to the procedure of Example 6B. The resultant product is isolated as described and crystallized from acetone-hexane to give 9 α -fluoro-11 β -hydroxyestradiol 3,17-diacetate.

Similarly, 9 β ,11 β -oxidoestradiol dicaproate and 9 β ,11 β -oxidoestradiol dipropionate (prepared from the corresponding ester of 9 α -bromo-11 β -hydroxyestradiol in the manner of Example 14A) are reacted with hydrofluoric acid to give 9 α -fluoro-11 β -hydroxyestradiol 3,17-dicaproate and 9 α -fluoro-11 β -hydroxyestradiol 3,17-dipropionate, respectively.

EXAMPLE 15

9 α -Chloro-11 β -Hydroxyestradiol 3,17-Diacetate

To a solution of 250 mg. of 9(11)-dehydroestradiol diacetate in 25 ml. of dioxane is added 100 mg. of N-chlorosuccinimide, 2.5 ml. of water and 1.0 ml. of 1.5 N perchloric acid. The reaction mixture is stirred in the dark for 48 hours, then poured into ice-water. The resultant gummy precipitate is dissolved in methylene chloride and crystallized by the addition of cold pentane to give 9 α -chloro-11 β -hydroxyestradiol 3,17-diacetate.

Alternatively, a solution of 100 mg. of 9 β ,11 β -oxidoestradiol diacetate in 10 ml. of chloroform is treated with anhydrous hydrogen chloride gas at -20° C. for 3 minutes, and then is kept at about 10° C. for 2 hours. The organic solution is washed with aqueous sodium acetate solution, then concentrated in vacuo to a residue which is crystallized from methylene chloride-pentane to give 9 α -chloro-11 β -hydroxyestradiol 3,17-diacetate.

EXAMPLE 16

9 α -11 β -Dichloroestradiol Diacylate

A. 9 α ,11 β -dichloroestradiol diacetate. — To a stirred,

cooled (-20°C.) solution of 9(11)-dehydroestradiol diacetate (354 mg.) in methylene chloride (15 ml.) and pyridine (0.4 ml.) is added chlorine (78 mg.) in carbon tetrachloride (1.5 ml.). The solution is stirred for 15 minutes at -20°C. , and for an additional hour at room temperature. The reaction mixture is then poured into water (300 ml.); the organic layer separated and washed successively with normal aqueous sodium thiosulphate, 5% aqueous sulphuric acid, 10% aqueous sodium bicarbonate, and water, dried (MgSO_4), and distilled in vacuo to a residue which is crystallized from acetone-hexane to give 9 α ,11 β -dichloroestradiol diacetate.

In a similar manner 9(11)-dehydroestradiol dicaproate and 9(11)-dehydroestradiol dipropionate are reacted with chlorine in carbon tetrachloride to give 9 α ,11 β -dichloroestradiol dicaproate and 9 α ,11 β -dichloroestradiol dipropionate, respectively.

B. 9 α ,11 β -dichloroestradiol dibenzoate. — Similarly, 9(11)-dehydroestradiol dibenzoate (478 mg.) in methylene chloride (15 ml.) and pyridine (4 ml.) is reacted with 78 mg. of chlorine in carbon tetrachloride (1.5 ml.) at -20°C. in the manner described in Example 16A. The resultant product is isolated in the described manner and recrystallized from ether-pentane to give 9 α ,11 β -dichloroestradiol dibenzoate.

EXAMPLE 17

9 α -Chloro-11 β -Fluoroestradiol Diaclyate

A. 9 α -chloro-11 β -fluoroestradiol diacetate. — To a stirred solution of 9(11)-dehydroestradiol diacetate (354 mg.) in carbon tetrachloride (15 ml.) and pyridine (2 ml.) is added hydrogen fluoride (200 mg.) in chloroform-tetrahydrofuran (3:1; 0.67 ml.) and N-chlorosuccinimide (146 mg.). Stirring is continued for 20 hours, and the reaction mixture is poured into 5% aqueous sodium carbonate solution (150 ml.) and extracted with methylene chloride. The organic extract is washed successively with water, 5% aqueous sulphuric acid, N-sodium thiosulphate and water, dried (MgSO_4) and evaporated in vacuo to a residue which is crystallized from ether-hexane to give 9 α -chloro-11 β -fluoroestradiol diacetate.

B. 9 α -chloro-11 β -fluoroestradiol dibenzoate. — 9(11)-dehydroestradiol dibenzoate is reacted with hydrogen fluoride and N-chlorosuccinimide in the manner of Example 17A to give 9 α -chloro-11 β -fluoroestradiol dibenzoate.

EXAMPLE 18

9 α -Bromo-11 β -Fluoroestradiol Diacetate

To a stirred solution of 9(11)-dehydroestradiol diacetate (354 mg.) in diethylacetic acid (15 ml.) is added N-bromoacetamide (152 mg.) followed immediately by hydrogen fluoride (200 mg.) in a solution of chloroform-tetrahydrofuran (3:1; 0.67 ml.). Stirring is continued for 18 hours and the reaction mixture is then poured into 10% aqueous sodium carbonate solution (150 ml.) and extracted with methylene chloride. The organic extract is washed with 5% aqueous sodium hydroxide and water, dried (MgSO_4), and evaporated to a residue which is crystallized from acetone-hexane to give 9 α -bromo-11 β -fluoroestradiol diacetate.

EXAMPLE 19

9 α -Bromo-11 β -Chloroestradiol Diacetate

To a stirred solution of 9(11)-dehydroestradiol diacetate (354 mg.) and lithium chloride (2.0 g.) in glacial acetic acid (15 ml.) is added N-bromoacetamide (152 mg.) followed at once by an anhydrous solution of hydrogen chloride (41 mg.) in tetrahydrofuran (0.3 ml.). Stirring is continued for three hours and the reaction mixture is then poured into water (200 ml.) and filtered. The residue on the filter is washed with water, dried and crystallized from ether-pentane to give 9 α -bromo-11 β -chloroestradiol diacetate.

EXAMPLE 20

9 α -Bromo-11 β -Acetoxyestradiol Diacetate

To a stirred solution of 9(11)-dehydroestradiol diacetate (354 mg.) and lithium acetate (1.5 g.) in glacial acetic acid (15 ml.) is added N-bromoacetamide (152 mg.). The reaction mixture is stirred for 18 hours at room temperature and is then poured into water (150 ml.). The resultant precipitate is filtered, dried, and crystallized from acetone-hexane to give 9 α -bromo-11 β -acetoxyestradiol diacetate (9 α -bromo-1,3,5(10)-estratriene-3, 11 β ,17 β -triol triacetate).

Similarly, 9(11)-dehydroestradiol dibenzoate is reacted with N-bromoacetamide and lithium acetate in acetic acid to give 9 α -bromo-11 β -acetoxyestradiol dibenzoate (9 α -bromo-1,3,5(10)-estratriene - 3,11 β ,17 β - triol 11-acetate 3,17-dibenzoate).

EXAMPLE 21

9 α -Chloro-11 β -Formyloxyestradiol Diacetate

To a stirred solution of 9(11)-dehydroestradiol diacetate (354 mg.) in formic acid (20 ml.; 98%) containing sodium formate (2.0 g.) is added N-chlorosuccinimide (146 mg.) and a solution of hydrogen chloride (41 mg.) in tetrahydrofuran (0.3 ml.). The mixture is stirred for 18 hours at room temperature and is then poured into water (200 ml.). The resultant precipitate is filtered, washed with water, dried and crystallized from acetone-hexane to give 9 α -chloro-11 β -formyloxyestradiol diacetate (9 α -chloro-1,3,5(10)-estratriene - 3,11 β ,17 β - triol 11-formate 3,17-diacetate).

EXAMPLE 22

9 α ,11 β -Dihaloogenestrone Methyl Ether

A. 9 α -chloro-11 β -fluoroestrone methyl ether. — A solution of 9(11)-dehydroestrone methyl ether (282 mg.) in carbon tetrachloride (15 ml.) and pyridine (2 ml.) is reacted with hydrogen fluoride (200 mg.) and N-chlorosuccinimide (146 mg.), in the manner of Example 17 to give 9 α -chloro-11 β -fluoroestrone methyl ether (9 α -chloro-11 β -fluoro-1,3,5(10)-estratriene-3-ol-17-one 3-methyl ether).

B. 9 α -bromo-11 β -fluoroestrone methyl ether. — A solution of 9(11)-dehydroestrone 3-methyl ether (282 mg.) in diethyl acetic acid (15 ml.) is reacted with N-bromoacetamide (152 mg.) and hydrogen fluoride (200 mg.), in the manner of Example 18, to give 9 α -bromo-11 β -fluoroestrone methyl ether.

C. 9 α -bromo-11 β -chloroestrone methyl ether. — A solution of 9(11)-dehydroestrone 3-methyl ether (282 mg.) in glacial acetic acid (15 ml.) is reacted with N-bromoacetamide (152 mg.) and hydrogen chloride (41 mg.) in the presence of lithium chloride (2.0 g.), in the manner of Example 19, to give 9 α -bromo-11 β -chloroestrone 3-methyl ether.

D. 9 α ,11 β -dichloroestrone methyl ether. — A solution of 1.0 g. of 9(11)-dehydroestrone methyl ether in carbon tetrachloride is allowed to react with 270 mg. of chlorine in the presence of pyridine according to the procedure of Example 9. The resultant product is crystallized from methylene chloride-pentane to give 9 α ,11 β -dichloroestrone 3-methyl ether.

EXAMPLE 23

9 α -Bromo-11 β -Acetoxyestrone 3-Methyl Ether

A solution of 9(11)-dehydroestrone 3-methyl ether (282 mg.) in glacial acetic acid (15 ml.) is reacted with N-bromoacetamide (152 mg.) in the presence of lithium acetate (2 g.) in the manner of Example 20, to give 9 α -bromo-11 β -acetoxyestrone 3-methyl ether.

EXAMPLE 24

9(11)-Dehydroestradiol 3-Benzoate

To a solution of 1.5 g. of 9(11)-dehydroestrone benzoate in 100 ml. of tetrahydrofuran is added a solution of 740 mg. of sodium borohydride in 3 ml. of water. The mixture is stirred for 1 hour, then poured into ice-water

11

and the solution acidified with acetic acid. The resulting precipitate is filtered, washed, dried, and crystallized from acetone-hexane to give 9(11)-dehydroestradiol 3-benzoate, M.P. 193–194° C.; $[\alpha]_D + 104^\circ$ (dioxane).

EXAMPLE 25

9 α ,11 β -Dichloroestradiol 3-Benzoate and the 17-Acetate Ester Thereof

A. *9 α ,11 β -dichloroestradiol 3-benzoate*.—9(11)-dehydroestradiol 3-benzoate (250 mg.) is reacted with 49 mg. of chlorine in the presence of pyridine according to the procedure of Example 9. The resultant product is crystallized from methylene chloride-pentane to give 9 α ,11 β -dichloroestradiol 3-benzoate (9 α ,11 β -dichloro-1,3,5(10)-estratriene-3,17 β -diol 3-benzoate).

B. *9 α ,11 β -dichloroestradiol 3-benzoate 17-acetate*.—The compound of Example 25A (100 mg.) is acetylated with acetic anhydride in pyridine according to the procedure of Example 11B. The resultant product is crystallized from methylene chloride-pentane to give 9 α ,11 β -dichloroestradiol 3-benzoate 17-acetate (9 α ,11 β -dichloro-1,3,5(10)-estratriene-3,17 β -diol 3-benzoate 17-acetate).

EXAMPLE 26

9 α -Chloro-11 β -Fluoro-17 α -Ethinylestradiol 3-Methyl Ether

9 α -chloro-11 β -fluoroestrone methyl ether (200 mg.) in dimethyl sulfoxide is reacted with sodium acetylide according to the procedure of Example 10 and the resultant product is isolated and purified as described to give 9 α -chloro-11 β -fluoro-17 α -ethinylestradiol 3-methyl ether (9 α -chloro - 11 β - fluoro-17 α -ethinyl-1,3,5(10)-estratriene-3,17 β -diol 3-methyl ether).

EXAMPLE 27

1-Methyl-9(11)-Dehydrostrone Methyl Ether

A. *1-methyl-9(11)-dehydrostrone*.—To a solution of 1.0 g. of 1,4,9(11)-androstatriene-3,17-dione in 40 ml. of acetic anhydride is added 250 mg. of p-toluene-sulfonic acid. The mixture is flushed with argon and heated on the steam bath for 5 hours, then poured into ice-water and stirred to hydrolyze any excess anhydride. The resulting 1-methyl-1,3,5-(10),9(11)-estratetraene-3-ol-17-one acetate is dissolved in 20 ml. of methanol, then a solution of 1 g. of potassium hydroxide in 2 ml. of water is added and the mixture heated under reflux for 20 minutes. The solution is poured into ice-water and acidified with hydrochloric acid. The resulting precipitate is filtered, washed with water, dried and crystallized from etherhexane to give 1-methyl-9(11)-dehydroestrone, M.P. 163–165° C.

$\lambda_{\text{max}}^{\text{MeOH}}$ 215 m μ (ϵ 24,100), 253 m μ (ϵ 12,100); $[\alpha]_D + 245^\circ$ (CHCl₃)

B. *1-methyl-9(11)-dehydrostrone methyl ether*.—To a solution of 500 mg. of the compound of Example 27A in 25 ml. methanol is added a solution of 3 g. potassium hydroxide in 5 ml. of water. The mixture is chilled and 2 ml. of dimethyl sulfate is added dropwise, then the mixture is stirred at room temperature for ½ hour. Additional 2 ml. portions of dimethyl sulfate are added at the next two ½ hour intervals, then the mixture is stirred a final ½ hour, and allowed to evaporate overnight. The resultant residue is washed with water, dried, and crystallized twice from ether-hexane to give 1-methyl-9(11)-dehydroestrone methyl ether; M.P. 100–102° C;

$\lambda_{\text{max}}^{\text{MeOH}}$ 213 m μ (ϵ 31,300), 252 m μ (ϵ 17,300); $[\alpha]_D + 262^\circ$ (CHCl₃)

EXAMPLE 28

1-Methyl-9(11)-Dehydrostrone Acetate

To a solution of 250 mg. of 1-methyl-9(11)-dehydroestrone in 5 ml. of pyridine is added 1 ml. of acetic anhydride and the mixture is allowed to stand at room tem-

12

perature for 22 hours. The mixture is then poured into ice-water, stirred to hydrolyze the excess anhydride and allowed to crystallize. The resultant solid is filtered and recrystallized from ether to give 1-methyl-9-(11)-dehydrostrone acetate, M.P. 125–126° C;

$\lambda_{\text{max}}^{\text{MeOH}}$ 212 m μ (ϵ 27,000), 247 m μ (ϵ 13,300); $[\alpha]_D + 215^\circ$ (CHCl₃)

EXAMPLE 29

1-Methyl-9(11)-Dihalogenoestrone Methyl Ether

A. *1-methyl-9 α ,11 β -dichloroestrone methyl ether*.—A solution of 1-methyl-9(11)-dehydrostrone 3-methyl ether (296 mg.) in carbon tetrachloride (15 ml.) and pyridine (0.4 ml.) is reacted with chlorine (78 mg.), in the manner of Example 9, to give 1-methyl-9 α ,11 β -dichloroestrone methyl ether.

B. *1-methyl-9 α -bromo-11 β -fluoroestrone methyl ether*.—A solution of 1-methyl-9(11)-dehydrostrone 3-methyl ether (296 mg.) in diethyl acetic acid (15 ml.) is reacted with N-bromoacetamide (152 mg.) and hydrogen fluoride (200 mg.), in the manner of Example 18, to give 1-methyl-9 α -bromo-11 β -fluoroestrone methyl ether.

C. *1-methyl-9 α -bromo-11 β -chloroestrone methyl ether*.—A solution of 1-methyl-9(11)-dehydroestrone 3-methyl ether (296 mg.) in glacial acetic acid (15 ml.) is reacted with N-bromoacetamide (152 mg.) and hydrogen chloride (41 mg.) in the presence of lithium chloride (2.0 g.), in the manner of Example 19, to give 1-methyl-9 α -bromo-11 β -chloroestrone methyl ether.

EXAMPLE 30

1-Methyl-9 α -Bromo-11 β -Hydroxyestrone Methyl Ether

A solution of 500 mg. of 1-methyl-9(11)-dehydroestrone methyl ether in dioxane is reacted with 240 mg. of N-bromoacetamide in the presence of water and perchloric acid according to the procedure of Example 13. The resultant product is crystallized from methylene chloride-pentane to give 1-methyl-9 α -bromo-11 β -hydroxyestrone methyl ether.

By subjecting the compound of this reaction to the sequence of reactions as described in Example 6 there is obtained 1-methyl-9 β ,11 β -oxidoestrone methyl ether from which is derived 1-methyl-9 α -fluoro-11 β -hydroxyestrone methyl ether and 1-methyl-9 α -chloro-11 β -hydroxyestrone methyl ether.

EXAMPLE 31

1-Methyl-9 α -Chloro-11 β -Fluoroestrone 3-Acetate

A solution of 1-methyl-9(11)-dehydroestrone 3-acetate (324 mg.) in carbon tetrachloride (15 ml.) and pyridine (2 ml.) is reacted with hydrogen fluoride (200 mg.) and N-chlorosuccinimide (146 mg.), in the manner of Example 17, to give 1-methyl-9 α -chloro-11 β -fluoroestrone 3-acetate.

EXAMPLE 32

1-Methyl-9 α -Bromo-11 β -Hydroxyestrone Acetate

A solution of 250 mg. of 1-methyl-9(11)-dehydroestrone acetate in dioxane is reacted with 110 mg. of N-bromoacetamide in the presence of water and perchloric acid according to the procedure of Example 13. The resultant product is crystallized from methylene chloride-pentane to give 1-methyl-9 α -bromo-11 β -hydroxyestrone 3-acetate.

EXAMPLE 33

1-Methyl-9 α -Fluoro-11 β -Hydroxyestrone Acetate

A. *1-methyl-9 β ,11 β -oxidoestrone acetate*.—A solution of 200 mg. of 1-methyl-9 α -bromo-11 β -hydroxyestrone acetate in acetone is heated with potassium acetate according to the procedure of Example 6A. The resultant product is crystallized from acetone-hexane to give 1-methyl-9 β ,11 β -oxidoestrone acetate.

B. *1-methyl-9 α -fluoro-11 β -hydroxyestrone acetate*.—A solution of 100 mg. of the compound of Example 33A

in methylene chloride is reacted with hydrofluoric acid according to the procedure of Example 6B. The resultant product is crystallized from acetone-hexane to give 1-methyl-9 α -fluoro-11 β -hydroxyestrone 3-acetate.

EXAMPLE 34

1-Methyl-9 α -Fluoro-11 β -Hydroxy-17 α -Ethinylestradiol 3-Acetate

1-methyl-9 α -fluoro-11 β -hydroxyestradiol 3-acetate (150 mg.) in dimethyl sulfoxide is allowed to react with sodium acetylide according to the procedure of Example 10 and the resultant product is isolated as described, then crystallized from acetone-hexane to give 1-methyl-9 α -fluoro-11 β -hydroxy-17 α -ethinylestradiol 3-acetate.

EXAMPLE 35

1-Methyl-9(11)-Dehydroestradiol and the 3,17-Di-Lower Alkanoates Thereof

A. *1-methyl-9(11)-Dehydroestradiol*.—A solution of 2.5 g. of 1-methyl-9(11)-dehydroestrone (compound 27A) in 50 ml. of methanol is chilled in ice. To the chilled solution 2.5 g. of sodium borohydride is added in portions and the resulting solution kept at 0° C. until foaming subsides. It is then allowed to stand at room temperature for 1 hour, acidified with 5% hydrochloric acid and diluted with water. The resulting product is crystallized from aqueous acetone to give 1-methyl-9(11)-dehydroestradiol, M.P. 148–152° C.;

$\lambda_{\text{max}}^{\text{MeOH}}$ 215 m μ (ϵ 25,000), 253 m μ (ϵ 13,200); $[\alpha]_D^{+138}$ (CHCl₃)

B. *1-methyl-9(11)-dehydroestradiol diacetate*.—A solution of 1.5 g. of the compound of Example 35A in 15 ml. of pyridine and 2 ml. of acetic anhydride is allowed to stand at room temperature for 18 hours, and is then poured into ice-water. The resulting precipitate is filtered and dried and crystallized twice from ether-hexane to give 1-methyl-9(11)-dehydroestradiol diacetate, M.P. 128–129° C.; $[\alpha]_D^{+78}$ (CHCl₃).

C. In a similar manner, by substituting other lower alkanic acid anhydrides, such as propionic and valeric acid anhydrides, for acetic anhydride in the above procedure, there are obtained the corresponding 3,17-dilower alkanoates, i.e., the 3,17-dipropionate and the 3,17-divalerate, respectively, of 1-methyl-9(11)-dehydroestradiol.

EXAMPLE 36

1-Methyl-9 α ,11 β -Dichloroestradiol Dipropionate

A solution of 300 mg. of 1-methyl-9(11)-dehydroestradiol dipropionate in carbon tetrachloride is reacted with 55 mg. of chlorine in the presence of pyridine according to the procedure of Example 9 to give 1-methyl-9 α ,11 β -dichloroestradiol dipropionate.

EXAMPLE 37

1-Methyl-9 α -Bromo-11 β -Hydroxyestradiol 3,17-Diacetate

A solution of 1-methyl-9(11)-dehydroestradiol diacetate (200 mg.) in dioxane is allowed to react with 80 mg. of N-bromo-acetamide in the presence of water and perchloric acid in the manner of Example 13 to give 1-methyl-9 α -bromo-11 β -hydroxyestradiol 3,17-diacetate.

EXAMPLE 38

17 α -Methyl-9(11)-Dehydroestradiol 3-Methyl Ether

To a stirred ethereal solution of methyl magnesium iodide (generated from magnesium metal (3 g.) and methyl iodide (7.5 ml.) in anhydrous ether (200 ml.)) is added a solution of 9(11)-dehydroestrone 3-methyl ether (1.0 g.) in tetrahydrofuran (50 ml.) dropwise, with stirring. The reaction mixture is then diluted by the addition of tetrahydrofuran (150 ml.), and the stirred mixture is distilled until 200 ml. of distillate has been collected. The reaction mixture is refluxed for one hour, cooled, and

carefully poured into cold 10% ammonium sulphate solution (200 ml.). The aqueous mixture is extracted with methylene chloride, and the organic extracts washed with water, dried (Na₂SO₄) and evaporated to a residue which is crystallized from acetone-hexane to give 17 α -methyl-9(11)-dehydroestradiol 3-methyl ether.

By following the above procedure, but substituting ethyl magnesium bromide (from ethyl bromide and magnesium metal in ether) for methyl magnesium iodide, the corresponding 17 α -ethyl compound is prepared, i.e., 17 α -ethyl-9(11)-dehydroestradiol 3-methyl ether.

EXAMPLE 39

1,17 α -Dimethyl-9(11)-Dehydroestradiol 3-Methyl Ether

1-methyl-9(11)-dehydroestrone 3-methyl ether is reacted with methyl magnesium iodide in a manner similar to that described in Example 38 to give 1,17 α -dimethyl-9(11)-dehydroestradiol 3-methyl ether.

Similarly by utilizing ethyl magnesium bromide instead of methyl magnesium iodide in the above reaction, there is obtained 1-methyl-17 α -ethyl-9(11)-dehydroestradiol 3-methyl ether.

EXAMPLE 40

17 α -Methyl-9(11)-Dehydroestradiol and the 1-Methyl Analog Thereof

A solution of 9(11)-dehydroestrone (2 g.) in tetrahydrofuran (100 ml.) is reacted with an ethereal solution of methyl magnesium iodide (prepared from magnesium metal (6 g.) and methyl iodide (15 ml.) in anhydrous ether (400 ml.)) in the manner of Example 38, to give 17 α -methyl-9(11)-dehydroestradiol.

In a similar manner, 1-methyl-9(11)-dehydroestrone (the compound of Example 27A) is reacted with methyl magnesium iodide to give 1,17 α -dimethyl-9(11)-dehydroestradiol.

EXAMPLE 41

17 α -Methyl-9(11)-Dehydroestradiol 3-Acetate and the 1-Methyl Analog Thereof

One gram of 17 α -methyl-9(11)-dehydroestradiol is allowed to react with acetic anhydride (1 ml.) in pyridine (10 ml.) at room temperature for 18 hours. The reaction mixture is diluted with water and the resultant precipitate filtered, washed with water, and dried to give 17 α -methyl-9(11)-dehydroestradiol 3-acetate.

In a similar manner, 1,17 α -dimethyl-9(11)-dehydroestradiol is reacted with acetic anhydride and pyridine to give 1,17 α -dimethyl-9(11)-dehydroestradiol 3-acetate.

EXAMPLE 42

9 α ,11 β -Dichloro-17 α -Methylestradiol 3-Methyl Ether

A solution of two hundred and ninety eight milligrams of 17 α -methyl-9(11)-dehydroestradiol 3-methyl ether in carbon tetrachloride (15 ml.) and pyridine (0.4 ml.) is allowed to react with chlorine (78 mg.) in the manner of Example 9, to give 9 α ,11 β -dichloro-17 α -methylestradiol 3-methyl ether.

In the same manner, but using as starting material 17 α -ethyl-9(11)-dehydroestradiol 3-methyl ether (Example 38) there is obtained 9 α ,11 β -dichloro-17 α -ethylestradiol 3-methyl ether.

EXAMPLE 43

1,17 α -Dimethyl-9 α ,11 β -Dichloroestradiol 3-Methyl Ether

A solution of three hundred and twelve milligrams of 1,17 α -dimethyl-9(11)-dehydroestradiol 3-methyl ether in methylene chloride (15 ml.) and pyridine (0.4 ml.) is allowed to react with chlorine (78 mg.) in the manner of Example 16A to give 1,17 α -dimethyl-9 α ,11 β -dichloroestradiol 3-methyl ether.

Similarly, by utilizing 1-methyl-17 α -ethyl-9(11)-dehydroestradiol 3-methyl ether as starting compound in the

15

procedure of this example, there is obtained 1-methyl-9 α , 11 β -dichloro-17 α -ethylestradiol 3-methyl ether.

EXAMPLE 44

9 α -Bromo-11 β -Hydroxy-17-Methylestradiol 3-Methyl Ether and the 1-Methyl Analog Thereof

A solution of five hundred milligrams of 17 α -methyl-9(11)-dehydroestradiol 3-methyl ether in dioxane (50 ml.) is allowed to react with N-bromoacetamide (242 mg.) in water (5.8 ml.) and 1.5 N-perchloric acid (2.3 ml.), in the manner of Example 13, to give 9 α -bromo-11 β -hydroxyestradiol 3-methyl ether.

In a similar manner, 1,17 α -dimethyl-9(11)-dehydroestradiol 3-methyl ether is reacted with N-bromoacetamide and perchloric acid to give 1,17 α -dimethyl-9 α -bromo-11 β -hydroxyestradiol 3-methyl ether.

EXAMPLE 45

9 α -Fluoro-11 β -Hydroxy-17 α -Methylestradiol 3-Methyl Ether

A. 9 β ,11 β -oxido-17 α -methylestradiol 3-methyl ether.—A solution of 300 mg. of 9 α -bromo-11 β -hydroxy-17 α -methylestradiol 3-methyl ether in acetone (20 ml.) is allowed to react with potassium acetate (600 mg.) in the manner of Example 6A to give 9 β ,11 β -oxido-17 α -methylestradiol 3-methyl ether.

B. 9 α -fluoro-11 β -hydroxy-17 α -methylestradiol 3-methyl ether.—A solution of five hundred milligrams of 9 β ,11 β -oxido-17 α -methylestradiol 3-methyl ether (the compound of Example 45A) in methylene chloride (20 ml.) is allowed to react with 48 percent aqueous hydrofluoric acid (2 ml.) in the manner of Example 6B to give 9 α -fluoro-11 β -hydroxy-17 α -methylestradiol 3-methyl ether.

Similarly, by subjecting 1,17 α -dimethyl-9 α -bromo-11 β -hydroxyestradiol 3-methyl ether to the sequence of reactions of Examples 45A and B, there is obtained 1,17 α -dimethyl-9 α -fluoro-11 β -hydroxyestradiol 3-methyl ether.

EXAMPLE 46

9 α -Chloro-11 β -Fluoro-17 α -Methyl Estradiol 3-Acetate

A solution of three hundred and ten milligrams of 17 α -methyl-9(11)-dehydroestradiol 3-acetate in carbon tetrachloride (15 ml.) and pyridine (2 ml.) is allowed to react with hydrogen fluoride (200 mg.) and N-chlorosuccinimide (146 mg.) in the manner of Example 17 to give 9 α -chloro-11 β -fluoro-17 α -methylestradiol 3-acetate.

EXAMPLE 47

1,17 α -Dimethyl-9 α -Bromo-11 β -Hydroxyestradiol 3-Acetate

A solution of five hundred milligrams of 1,17 α -dimethyl-9(11)-dehydroestradiol 3-acetate (the compound of Example 41) in dioxane (50 ml.) is allowed to react with N-bromoacetamide (213 mg.) in water (5.0 ml.) and 1.5 N-perchloric acid (2.0 ml.) in the manner of Example 13 to give 1,17 α -dimethyl-9 α -bromo-11 β -hydroxyestradiol 3-acetate.

EXAMPLE 48

1-Methyl-9 α -Bromo-11 β -Acetoxyestrone 3-Methyl Ether

1-methyl-9(11)-dehydroestrone 3-methyl ether in glacial acetic acid is reacted with N-bromoacetamide in the presence of lithium acetate in a manner similar to that described in Example 20 to give 1-methyl-9 α -bromo-11 β -acetoxy 3-methyl ether.

EXAMPLE 49

1 Methyl-9 α ,11 β -Dichloro-17 α -Ethynylestradiol 3-Methyl Ether

1-methyl-9 α ,11 β -dichloroestrone 3-methyl ether (prepared as described in Example 29A) is reacted with sodium acetylide in dimethyl sulfoxide in the manner described in Example 10. The resultant product is isolated

16

in the described manner to give 1-methyl-9 α ,11 β -dichloro-17 α -ethynylestradiol 3-methyl ether.

In a similar manner, 9 α -chloro-11 β -hydroxyestrone 3-acetate (the compound of Example 6), 9 α -bromo-11 β -acetoxyestrone 3-methyl ether (compound of Example 23) and 1-methyl-9 α -bromo-11 β -acetoxyestrone 3-methyl ether (the compound of Example 48) are each reacted with sodium acetylide in dimethylsulfoxide in the manner of Example 10 to give respectively 9 α -chloro-11 β -hydroxy-17 α -ethynylestradiol 3-acetate, 9 α -bromo-11 β -acetoxy-17 α -ethynylestradiol 3-methyl ether and 1-methyl-9 α -bromo-11 β -acetoxy-17 α -ethynylestradiol 3-methyl ether, respectively.

EXAMPLE 50

9 α -Bromo-11-Keto-17 α -Methylestradiol 17-Acetate and the 1-Methyl Analog Thereof

A. 17 α -methyl-9(11)-dehydroestradiol diacetate.—To 1 gram of 17 α -methyl-9(11)-dehydroestradiol (the compound of Example 40) in 10 ml. of pyridine is added 2 ml. of acetic anhydride. The reaction mixture is heated on the steam bath for 48 hours then cooled. Water is added and the aqueous mixture is extracted with ether. The extracts are combined, washed with 2 N hydrochloric acid and then with water, dried over sodium sulfate and evaporated in vacuo to a residue substantially of 17 α -methyl-9(11)-dehydroestradiol diacetate.

In a similar manner, 1,17 α -dimethyl-9(11)-dehydroestradiol is reacted with acetic anhydride in pyridine to give 1,17 α -dimethyl-9(11)-dehydroestradiol diacetate.

B. 9 α -bromo-11 β -hydroxy-17 α -methylestradiol 3,17-di-acetate.—17 α -methyl-9(11)-dehydroestradiol diacetate is reacted with N-bromosuccinimide and perchloric acid in a manner similar to that described in Example 4. The resultant product is isolated in the described manner to give 9 α -bromo-11 β -hydroxy-17 α -methylestradiol 3,17-di-acetate.

Similarly, 1,17 α -dimethyl-9(11)-dehydroestradiol diacetate is reacted with N-bromosuccinimide to give 1,17 α -dimethyl-9 α -bromo-11 β -hydroxyestradiol 3,17-di-acetate.

C. 9 α -bromo-11-keto-17 α -methylestradiol diacetate.—9 α -bromo-11 β -hydroxy-17 α -methylestradiol 3,17-di-acetate is reacted with chromic acid-sulfuric acid reagent in the manner described in Example 8. The resultant product is isolated as described to give 9 α -bromo-11-keto-17 α -methylestradiol diacetate.

Similarly, 1,17 α -dimethyl-9 α -bromo-11 β -hydroxyestradiol 3,17-di-acetate is reacted with chromic acid-sulfuric acid reagent to give 1,17 α -dimethyl-9 α -bromo-11-ketoestradiol diacetate.

D. 9 α -bromo-11-keto-17 α -methylestradiol 17-acetate.—A solution of 1 gram of 9 α -bromo-11-keto-17 α -methylestradiol diacetate in 30 ml. of 1% potassium carbonate in 90% aqueous methanol is left at room temperature for 2 hours. The solution is diluted with water. A solid separates which is filtered, dried, and crystallized from acetone-hexane to give 9 α -bromo-11-17 α -methylestradiol 17-acetate.

Similarly, 1,17 α -dimethyl-9 α -bromo-11-ketoestradiol diacetate is hydrolyzed with 1% potassium carbonate in aqueous methanol to give 1,17 α -dimethyl-9 α -bromo-11-ketoestradiol 17-acetate.

EXAMPLE 51

9 α -Halogeno-11-Ketoestradiol Derivatives

A. 1-methyl-9 α -bromo-11-ketoestradiol 3,17-di-acetate.—1-methyl-9 α -bromo-11 β -hydroxyestradiol diacetate (the compound of Example 37) is reacted with chromic acid-sulfuric acid reagent in the manner of Example 8 to give 1-methyl-9 α -bromo-11-ketoestradiol diacetate.

B. 9 α -chloro-11-ketoestradiol.—In a manner similar to that outlined in Example 8, 9 α -chloro-11 β -hydroxyestradiol diacetate (the compound of Example 15) is reacted with chromic acid-sulfuric acid reagent to give 9 α -chloro-11-ketoestradiol diacetate which, in turn, is hydrolyzed

with 1% potassium hydroxide in 90% aqueous methanol at room temperature for 24 hours yielding 9 α -chloro-11-ketoestradiol.

EXAMPLE 52

1 - Methyl - 9 α - Fluoro - 11 - Keto - 17 α - Ethinylestradiol 3 - Methyl Ether and 9 α Fluoro 11 - Keto - 17 α - Ethinylestradiol 3 - Acetate

A. 1-methyl-9 α -fluoro-11-ketoestrone 3-methyl ether.—In a manner described in Example 8, 1-methyl-9 α -fluoro-11 β -hydroxyestrone 3-methyl ether (prepared as described in Example 30) is reacted with chromic acid-sulfuric acid reagent and the resultant product isolated to give 1-methyl-9 α -fluoro-11-ketoestrone 3-methyl ether.

B. 1 - methyl - 9 α - fluoro - 11 - keto - 17 α - ethinylestradiol 3-methyl ether.—In a manner similar to that described in Example 10, 1-methyl-9 α -fluoro-11-ketoestrone 3-methyl ether is reacted with sodium acetylide in dimethylsulfoxide and the resultant product isolated and purified to give 1-methyl-9 α -fluoro-11-keto-17 α -ethinylestradiol 3-methyl ether.

In a similar manner, 9 α -fluoro-11-ketoestrone 3-acetate (the compound of Example 8) is reacted with sodium acetylide in dimethylsulfoxide and the resultant product isolated and purified to give 9 α -fluoro-11-keto-17 α -ethinylestradiol 3-acetate.

EXAMPLE 53

9 α -Bromo-11 β -Acetoxy-17 α -Methylestradiol 3-Acetate

In the manner similar to that described in Example 20 17 α -methyl-9(11)-dehydroestradiol 3-acetate (the compound of Example 41) is reacted with N-bromoacetamide and lithium acetate in glacial acetic acid and the resultant product isolated and purified as described to give 9 α -bromo-11 β -acetoxy-17 α -methylestradiol 3-acetate.

In a similar manner, 1,17 α -dimethyl-9(11)-dehydroestradiol 3-methyl ether (the compound of Example 39) is reacted with N-bromoacetamide and lithium acetate in acetic acid to give 1,17 α -dimethyl-9 α -bromo-11 β -acetoxyestradiol 3-methyl ether.

EXAMPLE 54

1-Methyl-9 α -Bromo-11 β -Acetoxyestradiol 3-Benzoate

A. 1-methyl-9(11)-dehydroestrone 3-benzoate.—In a manner similar to that described in Example 2, 1-methyl-9(11)-dehydroestrone (the compound of Example 27A) is reacted with benzoyl chloride in pyridine and the resultant product isolated to give 1-methyl-9(11)-dehydroestrone 3-benzoate.

B. 1-methyl-9(11)-dehydroestradiol 3-benzoate.—In a similar manner to that described in Example 11A 1-methyl-9(11)-dehydroestrone 3-benzoate in methanol is reacted with sodium borohydride and the resultant product isolated as described to give 1-methyl-9(11)-dehydroestradiol 3-benzoate.

C. 1 - methyl - 9 α - bromo - 11 β - acetoxyestradiol 3-benzoate.—In the manner of Example 20 the 9(11)-dehydroestradiol of Example 54B is reacted with N-bromoacetamide and lithium acetate in glacial acetic acid and the resultant product isolated as described to give 1-methyl-9 α -bromo-11 β -acetoxyestradiol 3-benzoate.

EXAMPLE 55

9 α -Fluoro-11 β -Hydroxyestradiol 17-Acetone

200 mg. of 9 α -fluoro-11 β -hydroxyestradiol 3,17-diacetate (the compound of Example 13) is dissolved in 10 ml. of a 1% solution of potassium carbonate (prepared from 1 gram of potassium carbonate in 90 ml. methanol and 10 ml. water). The solution is left at room temperature for 90 minutes, then water is added. A solid separates which is filtered, washed with water, then dried to give 9 α -fluoro-11 β -hydroxyestradiol 17-acetate.

In a similar manner other estradiol diacetates may be converted to the corresponding 3-ol-17-acetate as, for example, 1-methyl-9 α ,11 β -dichloroestradiol diacetate (the

compound of Example 36) upon reaction with potassium carbonate in methanol in the above described manner yields 1-methyl-9 α ,11 β -dichloroestradiol 17-acetate.

EXAMPLE 56

9 α -Chloro-11 β -Fluoroestradiol 17-Benzoate

200 mg. of 9 α -chloro-11 β -fluoroestradiol dibenzoate (the compound of Example 18) is dissolved in 10 ml. of a 1% solution of potassium carbonate (prepared from 1 gram of potassium carbonate in 90 ml. of methanol and 10 ml. of water). The solution is left overnight at room temperature then water is added. A solid separates which is filtered, washed with water and dried to give 9 α -chloro-11 β -fluoroestradiol 17-benzoate.

EXAMPLE 57

1-Methyl-9 α -Bromo-11 β -Acetoxyestradiol 3-Benzoate 17-Hemisuccinate

To 1 gram of 1-methyl-9 α -bromo-11 β -acetoxyestradiol 3-benzoate (the compound of Example 54) in 10 ml. of pyridine is added 1 gram of succinic anhydride. The reaction mixture is heated on a steam bath for 1 hour then cooled and diluted with water. A solid separates which is filtered, washed with water and dried to give 1-methyl-9 α -bromo-11 β -acetoxyestradiol 3-benzoate 17-hemisuccinate.

EXAMPLE 58

9 α -Chloro-11-Ketoestradiol 3,17-Di-Hemisuccinate and the Sodium Salt Thereof

A. 9 α -chloro-11-ketoestradiol 3,17-di-hemisuccinate.—In a manner described in Example 57 9 α -chloro-11-ketoestradiol (the compound of Example 51B) is reacted with succinic anhydride in pyridine and the resultant product isolated to give 9 α -chloro-11-ketoestradiol di-hemisuccinate.

B. 9 α -chloro-11-ketoestradiol 3,17-di-sodium hemisuccinate.—To 1 gram of 9 α -chloro-11-ketoestradiol 3,17-di-hemisuccinate suspended in 100 ml. of water is added 4.08 ml. of a 10% aqueous solution of sodium hydroxide. The resultant aqueous solution is evaporated in vacuo to a residue of substantially 9 α -chloro-11-ketoestradiol 3,17-di-sodium hemisuccinate.

EXAMPLE 59

9 α ,11 β -Dichloroestrone

9 α ,11 β -dichloroestrone 3-acetate (the compound of Example 3) is left overnight at room temperature with a 1% solution of potassium carbonate in a manner similar to that described in Example 56. The resultant product is isolated in the manner described to give 9 α ,11 β -dichloroestrone.

In a similar manner, other esters may be hydrolyzed to the corresponding free-hydroxy compound. For example, 9 α ,11 β -dichloro-17 α -ethinylestradiol 3-benzoate (the compound of Example 10) and 9 α -fluoro-11 β -hydroxyestrone 3-acetate (the compound of Example 6B) are each left overnight with 1% potassium carbonate and the respective resultant products isolated to give respectively 9 α ,11 β -dichloro-17 α -ethinylestradiol and 9 α -fluoro-11 β -hydroxyestrone.

EXAMPLE 60

9 α ,11 β -Dichloroestrone 3-Sulfate and the Potassium Salt Thereof

A. 9 α ,11 β -dichloroestrone 3-potassium sulfate.—A mixture of 1 gram of 9 α ,11 β -dichloroestrone (the compound of Example 59) and 1 gram of pyridine-sulfur trioxide complex in 10 ml. of pyridine is stirred at room temperature for 2½ hours. The mixture is then cooled in an ice bath and 1 ml. of 50% aqueous potassium hydroxide added rapidly with vigorous stirring. The mixture is stirred 2 minutes longer then allowed to cool to room temperature without stirring. The resultant two-

phase system is centrifuged at room temperature and the pyridine layer decanted. The aqueous residue is washed with pyridine and the pyridine wash is combined with the original pyridine layer. Ether is then added to the stirred pyridine solution until precipitation is complete. The mixture is then filtered and the residue dried to give substantially 9 α ,11 β -dichloroestrone 3-potassium sulfate.

B. 9 α ,11 β -dichloroestrone 3-sulfate.—0.5 gram of the 3-potassium sulfate ester of Example 60A is dissolved in 50 ml. of water and the solution brought to neutrality by adding hydrochloric acid. A solid results which is filtered and dried to give 9 α ,11 β -dichloroestrone 3-sulfate.

In a similar manner, other estratrienes of our invention may be converted to the sulfate ester. Thus, for example, 9 α -chloro-11 β -fluoroestradiol 17-benzoate (the compound of Example 56) upon reaction with pyridine-sulfur dioxide complex and isolation of the resultant product as described to give 9 α -chloro-11 β -fluoroestradiol 3-potassium sulfate 17-benzoate which is neutralized with hydrochloric acid to give 9 α -chloro-11 β -fluoroestradiol 3-sulfate 17-benzoate.

EXAMPLE 61

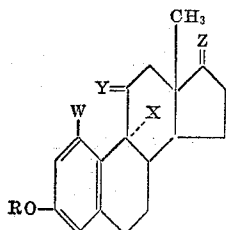
9 α ,11 β -Dichloroestradiol

To 500 mg. of 9 α ,11 β -dichloroestradiol diacetate (the compound of Example 16) is added 20 ml. of 1% potassium hydroxide in 90% aqueous methanol. The solution is left at room temperature for 24 hours, then diluted with water and made slightly acid by the addition of dilute hydrochloric acid. The resultant precipitate is filtered, washed with water, dried, and recrystallized from methylene chloride-pentane to give 9 α ,11 β -dichloroestradiol.

Similarly, other 17-acylate esters are hydrolyzed to the corresponding free hydroxy compound. For example, 9 α -fluoro-11 β -hydroxyestradiol dipropionate and 1-methyl-9 α ,11 β -dichloroestradiol 17-acetate are each hydrolyzed with 1% potassium hydroxide in aqueous methanol to give respectively 9 α -fluoro-11 β -hydroxyestradiol and 1-methyl-9 α ,11 β -dichloroestradiol.

We claim:

1. A compound selected from the group consisting of 1,3,5(10)-estratrienes having the following structural formula:



wherein R is a member selected from the group consisting of H, lower alkyl, and an acid radical of an acid selected from the group consisting of sulfuric acid and carboxylic acids having up to 8 carbon atoms; W is a member selected from the group consisting of H and methyl; X is a halogen having an atomic weight less than 100; Y is a member selected from the group consisting of keto,

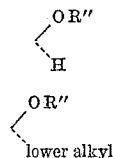


and



R' being a member selected from the group consisting of

H and lower alkanoyl and X' being a halogen of atomic weight less than 40 and when Y is X', the halogen X has an atomic weight greater than 20; and Z is a member selected from the group consisting of keto,



and



R'' being a member selected from the group consisting of H and lower alkanoyl.

2. 9 α -X-11 β -X'-1,3,5(10)-estratriene-3-ol-17-one wherein X is a halogen having an atomic weight greater than 20 and less than 100, and X' is a halogen having an atomic weight less than 40.

3. 3-lower alkyloxy-9 α -X-11 β -X'-1,3,5(10)-estratriene-17-one wherein X is a halogen having an atomic weight greater than 20 and less than 100, and X' is a halogen having an atomic weight less than 40.

4. 3-OR-9 α -X-11 β -X'-1,3,5(10)-estratriene-17-one wherein R is an acid radical of a carboxylic acid having up to 8 carbon atoms, X is a halogen having an atomic weight greater than 20 and less than 100, and X' is a halogen having an atomic weight less than 40.

5. 9 α ,11 β -dichloroestrone.

6. 9 α ,11 β -dichloroestrone acetate.

7. 9 α ,11 β -dichloroestrone benzoate.

8. 9 α -chloro-11 β -fluoroestrone 3-methyl ether.

9. 9 α -X-11 β -X'-17 α -ethinyl-1,3,5(10)-estratriene-3-ol-17-one wherein X is a halogen having an atomic weight greater than 20 and less than 100, and X' is a halogen having an atomic weight less than 40.

10. 3-OR-9 α -X-11 β -X'-17 α -ethinyl-1,3,5(10)-estratriene-17-one wherein R is an acid radical of a carboxylic acid having up to 8 carbon atoms, X is a halogen having an atomic weight greater than 20 and less than 100 and X' is a halogen having an atomic weight less than 40.

11. 3-lower alkyloxy-9 α -X-11 β -X'-17 α -ethinyl-1,3,5(10)-estratriene-17-one wherein X is a halogen having an atomic weight greater than 20 and less than 100, and X' is a halogen having an atomic weight less than 40.

12. 9 α ,11 β -dichloro-17 α -ethinylestradiol 3-benzoate.

13. 9 α ,11 β -dichloro-17 α -ethinylestradiol.

14. 9 α -chloro-11 β -fluoro-17 α -ethinylestradiol 3-methyl ether.

15. 9 α -X-1,3,5(10)-estratriene-3,11 β -diol-17-one wherein X is a halogen having an atomic weight less than 100.

16. 3-OR-9 α -X-1,3,5(10)-estratriene-11 β -ol-17-one wherein R is an acid radical of a carboxylic acid having up to 8 carbon atoms, and X is a halogen having an atomic weight less than 100.

17. 3-lower alkyloxy-9 α -X-1,3,5(10)-estratriene-11 β -ol-17-one wherein X is a halogen having an atomic weight less than 100.

18. 9 α -fluoro-11 β -hydroxyestrone 3-acetate.

19. 9 α -X-11 β -X'-estradiol wherein X is a halogen having an atomic weight greater than 20 and less than 100, and X' is a halogen having an atomic weight less than 40.

20. 9 α -X-11 β -hydroxyestradiol wherein X is a halogen having an atomic weight less than 100.

No references cited.

UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

Patent No. 3,076,829

February 5, 1963

Hans Reimann et al.

It is hereby certified that error appears in the above numbered patent requiring correction and that the said Letters Patent should read as corrected below.

Column 20, line 37, for "-3-ol-17-one" read -- -3,17 β -diol --; lines 41 and 47, for "17-one", each occurrence, read -- 17 β -ol --.

Signed and sealed this 3rd day of September 1963.

SEAL)
test:

ERNEST W. SWIDER
Testing Officer

DAVID L. LADD
Commissioner of Patents