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OXIDO-STEROIDS AND PROCESS FOR THEIR MANUFACTURE

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This invention relates to a process for the manufacture of 1:11α-oxido steroids and their conversion products. 1:11α-oxido steroids have not so far been described in the literature. This class of new compounds is of particular interest because opening of the oxide ring under certain conditions results in the formation of 1-dehydro-11α-hydroxy steroids, which constitutes a new approach to the therapeutically important 1-dehydro-corticoids, such as prednisone, prednisolone, 1-dehydro-aldosterone, dexamethasone, or to 1-dehydro-testosterone derivatives, such as the 1-dehydro-17α-methyl-testosterone which has an anabolic action.

The process of the present invention consists in treating an 11α-hydroxy-steroid, which contains no free hydroxyl group in position 20, with acyloxy radicals having an oxidising action and, if desired, in the resulting 1:11α-oxido-steroid the oxido group is opened up by treatment with an acid or, after formation of an oxo group in position 3, also by treatment with a base.

The conversion according to the present process of the 11α-hydroxy-steroids into 1:11α-oxido-steroids can be carried out with acyloxy radicals having oxidising action such as are obtained, more especially, by splitting metal acylates. Among the metal acylates may be mentioned more especially those of tetravalent lead in which the acyl radical is preferably derived from a lower aliphatic or aromatic acid, for example lead tetraacetate, lead tetrapropionate, lead tetrabutyrate, lead tetrabenzoate and the like. Likewise suitable are the complexes of mercury acylates and silver acylates such as mercury acetate, silver acetate or silver benzoate with iodine. The reaction is performed in a suitable solvent which is inert to the oxidising agent, such as hydrocarbons for example benzene. Particularly suitable are saturated hydrocarbons such as cyclohexane, above all methylcyclohexane, as well as dimethylcyclohexanes and the like, advantageously in the presence of a weak base, for example calcium carbonate. The process is advantageously performed at a temperature ranging from 50 to 150° C., but it can also be carried out at a temperature above or below this range.

Compounds suitable as starting materials for the present process are 11α-hydroxy compounds of the cholestane, cholane, coprostane, spirostane, furostane, cardanolide, pregnane and androstane series which may contain further substituents in the ring system and in the side chain, more especially in one or several of the positions 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 15, 16, 17, 18, 19, 20, 21, 22, such as esterified or etherified hydroxyl groups, free or more especially functionally converted, for example ketalized, oxo groups, functionally converted carboxyl groups, e.g. esterified or lactonised carboxyl groups, alkyl such as methyl groups, or halogen atoms. In the esters the acid radicals may be those of a lower aliphatic mono or dicarboxylic acid, preferably having from 1 to 10 carbon atoms, such as acetic, propionic, butyric, trimethyl-acetic, succinic, glutaric, glycollic and diglycollic acids, trifluoracetic acid or an aromatic carboxylic acid, preferably a monocyclic acid, such as benzoic acid, a monocyclic cycloaliphatic acid or araliphatic acid, such as hexahydrophthalic acids, tetrahydrophthalic acids, cyclohexanoic acids, cinnamic

acid, phenylpropionic acid, aliphatic or aromatic heterocyclic acids, such as furan carboxylic acid, nicotinic acid or also of sulfonic acids, such as methane sulfonic acid, benzenesulfonic, paratoluene sulfonic acid or the like. In the ethers the alcoholic radical is preferably one derived from a lower aliphatic alcohol, such as methyl, ethyl, propyl, butyl, isopropyl, isobutyl alcohol or of an araliphatic alcohol, such as a monocyclic lower araliphatic alcohol e.g. benzyl alcohol or of heterocyclic alcohols, such as tetrahydropyranol or the like. Among the compounds having ketalized or acetalized oxo groups there are especially to be mentioned those which have oxo groups ketalized or acetalized with a lower divalent aliphatic alcohol, such as ethylene glycol, propylene glycol and the like. Furthermore, the starting materials may contain double bonds, for example, starting from carbon atom 5. Examples of specific starting materials are

3β-acyloxy-11α-hydroxy-cholestane,
11α-hydroxy-tigogenine acylates,
11α-hydroxy-diosgenine acylates,
sarmentogenine-3-acetate,
3α-acyloxy-11α-hydroxy-20-ethylenedioxy-5β-pregnane,
3β-acyloxy-11α-hydroxy-20-ethylenedioxy-5α-pregnane,
Δ^5-3β-acyloxy-11α-hydroxy-20-ethylenedioxy-pregnene,
Δ^5-3:20-bis-ethylenedioxy-11α-hydroxy-pregnene,
Δ^5-3:20-bisethylene-dioxy-11α-hydroxy-21-acyloxy-pregnene,
Δ^5-3:20-bisethylene-dioxy-11α:17α-dihydroxy-21-acyloxy-pregnene,
Δ^5-3β:17β-diacyloxy-11α-hydroxy-androstene,
3β:17β-diacyloxy-11α-hydroxy-5α-androstane,
Δ^5-3-ethylenedioxy-11α-hydroxy-17β-acyloxy-androstene,
Δ^5-3-ethylenedioxy-11α-hydroxy-17β-acyloxy-17α-methyl-androstene,
Δ^5-3:17-bisethylenedioxy-11α-hydroxy-androstene,
Δ^5-3-ethylenedioxy-11α-hydroxy-17β-acyloxy-17α-methyl-19-nor-androstene and the like.

The oxidation of the 11α-hydroxy-steroids according to the present process leads as a rule to mixtures of the 1α:11α-epoxides and 1β:11α-epoxides in which mixture depending on whether the rings A and B are cis-linked or trans-linked one or the other kind of isomer preponderates.

For the conversion of epoxides into the 1-dehydro-steroids especially the 1α:11α-oxido-steroids are suitable.

Hitherto the 1:2-double bond has been introduced either by bromination and dehydrobromination or by dehydrogenation with selenium dioxide, or by microbiological methods. The present process enables the 1:2-double bond to be introduced in a completely novel manner. The 1α:11α-oxido-steroids obtained by the present process can be opened up hydrolytically or acylolytically under the action of acids to form 1:11α-diols, monoacylates or diacylates thereof or halohydrins. When the steroid used for splitting the oxide contains an oxo group in position 3 or when such a group is formed during the splitting, for example from a 3-ketal, the corresponding 1-dehydro-11α-hydroxy compounds are obtained directly.

The 1:11α-oxides of the compounds having no free or protected oxo group in position 3 are opened up for example by means of aliphatic carboxylic acids, such as formic acid, acetic acid, propionic acid, trichloroacetic acid, trifluoroacetic acid, or in the case of a weak acid if desired with addition of a strong acid, such as sulfuric or para-toluenesulfonic acid. These agents yield above all monoacylates of the 1:11-diols. When the reaction is performed with a hydrohalic acid, for example hydrogen chloride or hydrogen bromide, in a diluent such as glacial acetic acid, dioxane, methanol or the like, there are obtained 1-halogeno-11α-hydroxy-compounds whereas under the action of an acylhalide, for example acetyl bromide,

1-halogeno-11α-acyloxy-steroids are formed. In a medium free from hydroxyl group the main products formed are derivatives of $\Delta^{9(11)}$-1-hydroxy-steroids; for example, boron trifluoride etherate or para-toluenesulfonic acid in acetanhydride or propionic anhydride yields the $\Delta^{9(11)}$-1-acetates and $\Delta^{9(11)}$-1-propionates respectively.

When the 1α:11α-oxide subjected to the scission contains a free or protected oxo group in position 3, the opening of the oxide is extremely easy and occurs, for example, even by simple heating with glacial acetic acid in the presence or absence of sodium acetate or potassium acetate. In this manner the Δ^1-3-oxo-11α-hydroxysteroids are formed. When a free 3-oxo-group is present, the scission of the ether ring also takes place under basic conditions, for example already by treating with alkali metal salts of aliphatic carboxylic acids, such as sodium acetate, potassium acetate, potassium propionate and the like. There are also suitable alkali metal alcoholates, bicarbonates, carbonates and hydroxides, for example sodium methylate, potassium isopropylate, potassium tertiary butylate, sodium bicarbonate, potassium carbonate, sodium hydroxide and the like; but also alkaline earth metal hydroxides, such as barium hydroxide, calcium hydroxide. Furthermore, there may also be used aluminum alcoholates, for example aluminum isopropylate or tertiary butylate, or tertiary aliphatic or cycloaliphatic amines, such as triethylamine, N-methylpiperidine, N-methyl-morphdine and the like. Scission can also be performed by chromatography on aluminum oxide. The above-mentioned bases are used in suitable solvents in which the oxido compound and also the base is soluble, for example lower aliphatic alcohols, cyclic ethers or aromatic hydrocarbons or mixtures of these compounds.

When a Δ^5-3-ketal is used as starting material, the protected group in the 3-position of a resulting Δ^5-1:11α-oxido-3-ketal can be split by mild acid treatment, for example with para-toluene sulfonic acid in acetone, or by a short warming with dilute acetic acid whereby surprisingly, not the Δ^4-3-ketones are formed—as in the case with compounds not containing a 1:11α-oxido group—but the Δ^5-1:11α-oxido-3-ketones. When the latter products are subjected to a mild alkaline treatment, for example with alumina, they are converted into the $\Delta^{1:5}$-3-oxo-11α-hydroxy compounds which in their turn are easily isomerized for example by heating with acetic acid or by prolonged adsorption on alumina, to form the corresponding $\Delta^{1:4}$-3-ketones.

As by-products of the described reaction of 11α-hydroxy-steroids with metal acylates having an oxidizing action there are obtained 9:11-seco-11-nor-compounds in varying yield. For example, Δ^5-3:20-bisethylenedioxy-11α-hydroxy-pregnene yields Δ^5-3-ethylenedioxy-20-oxo-9:11-seco-11-nor-pregnene with simultaneous hydrolysis of the ketal at carbon atom 20. By subsequent treatment with dilute acetic acid the 9:11-seco-11-nor-progesterone is obtained. The 3:20-dioxo-9:11-seco-11-nor-pregnane compounds have a progestative, anti-estrogenic, and blood pressure-regulating action.

In contrast to their 1α-epimers, the 1β:11α-oxido-steroids, under the influence of acids, yield, particularly in the presence of a ketal or carbonyl function at carbon atom 3, apart from 1-dehydro-3-oxo-11α-hydroxysteroids, mainly Δ^1-2:3-seco-11α-hydroxy-steroids, the ring A being split up during the formation of the latter compound. For example, 1β:11α-oxido-3:20-bis - ethylenedioxy-5α-pregnane yields on treatment with sulfuric acid in methanol the methyl ester of Δ^1-2:3-seco-11α-hydroxy-20-oxo-5α-pregnane-3-acid. When dilute acetic acid, a mixture of sodium acetate and glacial acetic acid, or para-toluenesulfonic acid in acetone is used for hydrolysis, the corresponding glycol ester is obtained in place of the methyl ester. Hydrolysis of Δ^5-1β:11α-oxido 3:20-bisethylenedioxy-pregnene yields in addition to the $\Delta^{1:5}$-2:3-seco-11α-hydroxy-compound also 1-dehydro-11α-hydroxy-progesterone.

The 2:3-seco compounds, on treatment with concentrated sulfuric acid, in part yield 1-dehydro-3-oxo-steroid compounds, re-cyclization occurring.

Of the 1:11α-oxido steroids of the pregnane series obtainable by the process of this invention, those merit special mention which are oxygenated in 3- and 18-position, in particular those which have an 18-positioned carboxylic acid group lactonized with a 20-hydroxyl group. Such 3-oxygenated 18:20-lactones of 1:11α-oxido-20-hydroxy-preganane-18-acids, as e.g. the 18:20-lactones of Δ^4-3-oxo-1α:11α-oxido-20β-hydroxy-pregnene-18-acids or their 3-ketals can be converted, after opening up the 1:11α-epoxide ring by the process of this invention, or by way of the 2:3-seco compounds mentioned, into the corresponding 1-dehydro-18:20-lactones of 20-hydroxy-pregnene-18-acids. Compounds of this kind are suitable as intermediate products for the manufacture of physiologically active 1-dehydrocorticoids having an oxygen function in 18-position. The conversion of the aforementioned 1-dehydro-18:20-lactones of 20-hydroxy-pregnene-18-acids can be illustrated as follows: The 18:20-lactone of 3-oxo-11α:20β-dihydroxy-$\Delta^{1:4}$ - pregnadiene - 18 - acid obtainable by the process of this invention is converted into the 11β:18-lactone of 3-oxo-11β:20β-dihydroxy-$\Delta^{1:4}$-pregnadiene-18-acid by treatment of its tosylate with a base, e.g. potassium carbonate, the 20-hydroxyl group of the conversion product dehydrogenated to form the oxo group, and an acyloxy group introduced in 21-position in per se conventional manner; after ketalization of the 20-oxo group, the carbonyl groups at carbon atoms 3 and 18 are treated with the quantity of lithium aluminum hydride calculated for the conversion of the lactone group in 18:11-position into an 18:11-cyclosemiacetal group and for the reduction of the 3-oxo-group, after which the 3-hydroxy group is selectively re-oxidized under the conditions of the Oppenauer reaction, and the 20-ketal group of the resulting product is hydrolyzed under acid conditions. In this manner the 1-deyhdro-aldosterone is obtained.

In a similar manner, the 18:20-lactones of $\Delta^{1:5}$-3-oxo-11α:20-dihydroxy-steroid-18-acids obtainable by the process of this invention, especially those of the pregnane series, can be converted by selective reduction of the 1:2-double bond, followed by isomerization, into the 18:20-lactones of Δ^4-3-oxo-11:20-dihydroxy-pregnane-18-acids which in turn can be converted into the 11β:18-lactones of Δ^4-3,20-dioxo-11β-hydroxy-pregnene-18-acids by the method described above. These latter products are known intermediates for the manufacture of aldosterone or derivatives thereof.

The following examples illustrate the present process.

Example 1

1.480 grams of Δ^5-3:20-bisethylenedioxy-11α-hydroxy-pregnene (melting at 215–217°C.; obtained by ketalising 11α-hydroxy-progesterone) are added to a stirred suspension previously boiled for 15 minutes of 1.5 grams of calcium carbonate and 4.5 grams of lead tetraacetate in 150 cc. of methyl-cyclohexane, and the reaction mixture is refluxed for 18 hours, filtered, the filter residue is washed with ethyl acetate and ether, the filtrate is shaken once with 40 cc. of potassium iodide solution of 5% strength, once with 40 cc. of sodium sulfite solution of 10% strength and three times with water, dried and evaporated. There are obtained 2.09 grams of a substantially crystalline residue. One recrystallization from a mixture of methylene chloride and petroleum ether yields 620 mg. of a Δ^5-3:20-bisethylene- dioxy-1α:11α-oxido-pregnene melting at 203–208° C. Elution of the mother liquors by chromatography on alumina yields another 174 mg. of the same compound which melts at 213–214° C. after having been twice recrystallized. The infra-red spectrum of the compound contains no absorption bands in the OH and CO regions. Subsequent chromatogram fractions yield 105 mg. of Δ^5-3:20-bisethylenedioxy-1β:11α-oxido-

pregnene melting at 185–188° C. which is isomeric with the above compound at carbon atom 1. A mixed melting point test of the two isomers produces a very minor depression, but their infra-red spectra differ. By careful chromatography about 50 mg. more of starting material can be eluted.

From the fractions eluted with a mixing of petroleum ether and benzene Δ^5-3-ethylenedioxy-20-oxo-9:11-seco-11-nor-pregnene is isolated. After being recrystallized three times from a mixture of methylene chloride and hexane the product melts 148–149° C.; optical rotation $[\alpha]_D=+11.2\pm1°$. In the nuclear magnetic resonance spectrum of the compound, signals occur inter alia at 321, 238, 128, 78, 67 and 47 Hertz units of frequency (obtained in deuterochloroform with tetramethylsilane as internal reference). After hydrolysing the ketal grouping at carbon atom 3 by means of para-toluenesulfonic acid in acetone, there is obtained 9:11-seco-11-nor-progesterone melting at 89–90° C. In the nuclear magnetic resonance spectrum of the compound signals occur inter alia at 343, 130, 73 (corresponding to 6 protons) and 49 Hertz units of frequency.

Example 2

300 mg of Δ^5-3:20-bisethylenedioxy-1*a*:11*a*-oxido-pregnene in 12 cc. of acetone are treated with 50 mg. para-toluenesulfonic acid and the whole is stirred at room temperature until all has passed into solution and the solution is kept for 14 hours, diluted with water, cooled to 0° C., and the precipitated Δ^5-3:20-dioxo-1α:11α-oxido-pregnene is filtered off and washed with water. One recrystallization from a mixture of methylene chloride and petroleum ether yields 95 mg. of the product which crystallizes in lustrous flakes and melts at 194-198° C. (uncorrected). The infra-red spectrum of the product displays an absorption band at 5.88μ. When the acetone is distilled off the aqueous filtrate under reduced pressure at about 60° C., the concentrated filtrate is saturated with sodium chloride and subjected to a conventional extraction with ether+methylene chloride (3:1), 132 mg. of a partially crystalline oil are obtained which yields on crystallization from ether 67 mg. of $\Delta^{1:4}$-3:20-dioxo-11α-hydroxy-pregnadiene. The melting point, mixed melting point and infra-red spectrum of this product are identical with those of the product described in Example 3. The mother liquor contains a mixture of the aforementioned Δ^5-1:11α-ether and 11α-hydroxy-diene.

Example 3

50 mg. of Δ^5-3:20 - bisethylenedioxy - 1α:11α-oxido-pregnene are dissolved with heating in 5 cc. of acetic acid 80% strength, 30 mg. of sodium acetate are added, and the whole is heated for 2 hours at 100° C. The mixture is kept for 15 hours at room temperature, diluted with 20 cc. of water, saturated with sodium chloride and worked up with ether+methylene chloride (3:1). When the isolated oil (32 mg.) is sprinkled with ether, it crystallizes. Two crystallizations from a mixture of methylene chloride, ether and petroleum ether yields $\Delta^{1:4}$-3:20-dioxo-11α-hydroxy pregnadiene in fine needles melting at 220–220.5° C. Optical rotation $[\alpha]_D=+102.4°\pm0.8°$ (c.=1.03 in chloroform). Absorption maximum at 248 mμ (ϵ=21,000). The infra-red spectrum of the compound in Nujol contains absorption bands at 2.90, 5.85, 6.03, 6.16 and 6.25μ.

Example 4

100 mg. of Δ^5 - 3:20-bisethylenedioxy-1α:11α-oxido-pregnene are dissolved in 3:5 cc. of acetic acid of 80% strength by being heated to 60° C., the solution is maintained for a total of 5 minutes at the same temperature and then kept for 30 minutes at room temperature. The reaction mixture is diluted with water, saturated with sodium chloride and extracted with ether. The extracts are washed with sodium bicarbonate solution and with water until neutral, dried and evaporated. The crude product is a mixture of Δ^5 - 3 - ethylenedioxy-1α:11α-oxido - 20 - oxo - pregnene and Δ^5-3:20-dioxo-1α:11α-oxido - pregnene (strong absorption band in the infra-red spectrum at 5.87-5.89μ). Subsequent chromatography on alumina yields the former compound in pure form melting at 135–139° C. However, during the chromatography Δ^5 - 3:20 - dioxo - 1α:11α-oxido-pregnene is converted into the isomeric $\Delta^{1:5}$-3:20-dioxo-11α-hydroxy-pregnadiene melting at 172–175° C. $\lambda_{max.}$:228 mμ, ϵ=11,600. Infra-red absorption bands in methylene chloride: 5.87μ, 5.94μ and 6.24μ.

Example 5

3.0 g. of dried calcium carbonate and 10.0 g. of pre-dried lead-IV-acetate in 300 ml. of cyclohexane are heated for 15 minutes at 80° C. with stirring. After that, 3.0 g. of 3:20-bisethylenedioxy-11α-hydroxy-5β-pregnane are added and the mixture stirred for 17 hours while being refluxed. The course of the reaction is watched preferably by hydrolyzing test portions by means of a mixture of glacial acetic acid and sodium acetate and determination of the extinction of the resulting α,β-unsaturated ketone in the U.V. spectrum. The cooled reaction solution is filtered and the residue thoroughly washed with ether. The combined filtrates are extracted by agitation in turn with 200 ml. of water, 100 ml. of 5% potassium iodide solution, 100 ml. of 10% sodium sulfite solution, and then three times with 100 ml. of water each time. On drying the solution and evaporating the solvent under reduced pressure, 3.10 g. of a colorless foam are obtained. Chromatographic purification over alumina yields 2.24 g. of pure 3:29-bisethylenedioxy-1α,11α-oxido-5β-pregnane in the form of a foam. In the IR-spectrum of the compound, absorption bands are observed inter alia at 7.55μ, 9.20μ, 9.30μ, 9.50μ, 9.66μ, 10.00μ, 10.55μ, 11.00μ and 11.45μ.

In the same manner the 3:20-bisethylenedioxy-11α-hydroxy-21-acetoxy-5β-pregnane obtainable by ketalization from 3:20 - dioxo - 11α-hydroxy-21-acetoxy-5β-pregnane may also be converted into 3:20 - bisethylenedioxy-1α:11α-oxido-21-acetoxy-5β-pregnane.

Example 6

3.8 g. of 3:20-bisethylenedioxy-11α-hydroxy - 5α-pregnane are added to a suspension—which has been heated at 100° C. for 15 minutes—of 3.8 g. of calcium carbonate and 12.7 g. of lead-IV-acetate in 380 ml. of methylcyclohexane, and the whole stirred for 14 hours while being refluxed. Another 5.0 g. of lead-IV-acetate then added and boiling continued for 3 more hours. Working up in the same manner as in Example 5 yields 5.1 g. of a crystallizate mixed with an oil having an aromatic odor. Recrystallization twice from a mixture of methylene chloride and petroleum ether yields 1.51 g. of 3:20-bis-ethylenedioxy-1β,11α-oxido-5α-pregnane of melting point 203–206° C. Chromatographic purification of the mother liquors yields 1.12 g. of the same product. $[\alpha]_D$:+4.0° (c.=0.75, in $CHCl_3$). The infrared spectrum shows bands inner alia at 7.30μ, 7.56μ, 8.25μ, 8.41μ, 8.55μ, 9.57μ, 10.03μ, 10.56μ, 11.53μ and 11.72μ.

The 11α-hydroxy-3:20-diketals of 5α and 5β-pregnane, respectively, used as starting materials in Examples 5 and 6 are obtained from the corresponding 3α and 3β:11α-diacetoxy-20-oxo compounds by partial hydrolysis of the 3-acetates, oxidation by means of N-bromacetamide to the 3:20-diketone, ketalization, and subsequent alkaline hydrolysis of the 11α-acetate.

Example 7

200 ml. of cyclohexane, 2.0 g. of calcium carbonate, and 7.0 g. of lead-IV-acetate are heated to 80° C. for a short while, then treated with 1.50 g. of Δ^5-3-ethylenedioxy-11α-hydroxy-17β-acetoxy-17α-methyl - androstene (prepared by partial hydrolysis of Δ^5-3-ethylenedioxy-

11α,17β-diacetoxy-17α-methyl-androstene obtained from Δ^4-3-oxo-11α:17β-dihydroxy-17α-methyl - androstene by acetylation and ketalization). The mixture is refluxed with stirring for 16 hours. Working up in the usual manner (see Example 5) yields 1.85 g. of a crystalline crude prduct, By crystallization from a mixture of ether and petroleum ether the pure Δ^5-3-ethylenedioxy-1ξ:11α-oxido-17β-acetoxy-17α-methyl-androstene of melting point 185–188° C. is obtained.

An analogous treatment of Δ^5-3-ethylene-dioxy-11α-hydroxy-17β-acetoxy - androstene with lead-IV-acetate yields a mixture of the two oxido compounds epimeric at carbon atom 1: Δ^5-3-ethylenedioxy-1α:11α- and Δ^5-3-ethylenedioxy-1β:11α-oxido-17β-acetoxy-androstene.

Example 8

9.0 g. of 18:20-lactone of Δ^5-3-ethylenedioxy-11α:20β-dihydroxy-pregnene-18-acid are stirred into a suspension, heated to 100° C., of 9.0 g. of calcium carbonate and 30.0 g. of lead-IV-acetate in 900 ml. of methylcyclohexane and the mixture boiled under reflux. After 1 hour another 10.0 g. of lead-IV-acetate and 5.0 g. of calcium carbonate are added, and after 13 hours another 10.0 g. of lead-IV-acetate. After a total of 15 hours, the reaction is stopped and the product worked up. There are obtained about 12 g. of an oily product which is resolved into four components by chromatography over alumina (activity II).

Yields of 1 to 2% are obtained of the 18:20-lactone of Δ^5 - 3 - ethylenedioxy - 11 - oxo - 20β - hydroxy - pregnene-18-acid. The following compounds are subsequently separated: an about 15% yield of the 18:20-lactone of Δ^5-3-ethylenedioxy - 9:11 - seco - 11 - nor - 20β - hydroxy-pregnene-18-acid of melting point 186–190° C. which is converted by deketalization into the 18:20-lactone of Δ^4 - 3 - oxo - 9:11 - seco - 11 - nor - 20β - hydroxy-pregnene-18-acid; a 20–25% yield of the 18:20-lactone of Δ^5 - 3 - ethylenedioxy - 1α:11α - oxido - 20β - hydroxy-pregnene-18-acid of melting point 160° C. (bands in the IR spectrum at 5.72μ, 6.95μ, 7.30μ, 7.50μ, 7.70μ, 8.75μ, 8.86μ, 9.00μ, 9.25μ, 9.62μ, 9.80μ, 10.03μ, 10.35μ, and 10.53μ), and an about 20% yield of 18:20-lactone of Δ^5 - 3 - ethylenedioxy - 1β:11α - oxido - 20β - hydroxy-pregnene-18-acid of melting point 205–209° C. (bands in the IR spectrum at 5.70μ, 6.92μ, 7.30μ, 7.45μ, 7.68μ, 8.20μ, 8.80μ, 9.02μ, 9.20μ, 9.80μ, 10.18μ, 10.55μ, 10.75μ and 10.95μ).

Example 9

In a manner analogous to that described in the preceding example, there are obtained from 3β-acetoxy-11α-hydroxy-5α-spirostane and 3β-acetoxy-11α-hydroxy-cholestane with lead-IV-acetate 3β-acetoxy-1ξ:11α-oxido-5α-spirostane and 3β-acetoxy-1ξ:11α-oxido-5α-cholestane respectively.

Example 10

210 mg. of 3:20-bisethylenedioxy-1α:11α-oxido-5β-pregnane are dissolved in 20 ml. of glacial acetic acid, treated with 200 mg. of crystalline sodium acetate, and refluxed for two hours. The reaction solution is diluted with benzene and evaporated under reduced pressure. The residue is dissolved in water and ether, and the organic layer washed neutral with sodium bicarbonate and water. The ethereal solution is dried and evaporated under reduced pressure. It gives a quantitative yield of 1-dehydro-3:20-dioxo-11α-hydroxy-5β-pregnane. The product is recrystallized twice from methylene chloride+petroleum ether and then melts at 198–199° C. $[\alpha]_D = +174.5 \pm 1.2$ (chloroform). In the IR spectrum bands at 2.75–2.90μ, 5.88μ, 5.98μ, 6.25μ, 7.22μ, 7.30μ, 7.40μ, 8.20μ, 8.66μ, 9.00μ, 9.50μ, 10.18μ, and 11.88μ.

Example 11

200 mg. of 3:20-bisethylenedioxy-1α:11α-oxido-5β-pregnane, 20 ml. of glacial acetic acid and 200 mg. of crystalline sodium acetate are heated at 80° C. for 4 minutes. The reaction mass is then diluted with benzene, and the solvent expelled under reduced pressure. Working up as in Example 10 yields 183 mg. of 3-ethylenedioxy-1α:11α-oxido-20-oxo-5β-pregnane which after being recrystallized from a mixture of methylene chloride and petroleum ether melts at 169–170° C. $[\alpha]_D = +93.8° \pm 1.0°$ C. (c.=1.027, in chloroform). (Bands in the IR spectrum inter alia at 5.88μ, 7.25μ, 7.40μ, 7.50μ, 7.65μ, 8.50μ, 9.02μ, 9.20μ, 9.30μ, 9.65μ, 9.98μ, 10.55μ, 11.00μ, 11.45μ and 11.75μ.)

Example 12

150 mg. of 3:20-bisethylenedioxy-1β:11α-oxido-5α-pregnane are dissolved in 10 ml. of acetone and, after the addition of 25 mg. of para-toluene-sulfonic acid monohydrate, allowed to stand at room temperature for 18 hours. The solution is neutralized with a few drops of saturated sodium bicarbonate solution, concentrated under reduced pressure at 40° C., diluted with ether, and washed three times with water. On evaporation of the solvent there are obtained 138 mg. of crystalline glycol ester of 2,3 - seco - Δ^1 - 11α - hydroxy - 20 - oxo - 5α - pregnene-3-acid of melting point 103–104° C. After being recrystallized twice from a mixture of methylene chloride and petroleum ether, the compound melts at 105–106° C. $[\alpha]_D = +67.0 \pm 1.2°$ C. (c.=1.0, in $CHCl_3$). The IR spectrum exhibits inter alia bands at 2.82μ, 5.78μ, 5.87μ, 6.15μ, 7.38μ, 8.50μ, 9.81μ and 10.80μ. The same product is obtained by treating 3:20-bis-ethylenedioxy-1β:11α-oxido-5α-pregnane with glacial acetic acid+sodium acetate or dilute acetic acid.

By hydrogenation of 150 mg. of Δ^1-glycol ester in rectified alcohol with palladium black and recrystallization from a mixture of ether and hexane there are obtained 130 mg. of the glycol ester of 2:3-seco-11α-hydroxy-20-oxo-5α-pregnane - 3 - acid. Double melting point at 92° C. and 107–108° C.; optical rotation $[\alpha]_D^{27} = +43.2 \pm 1.8°$ (c.=0.560).

Example 13

400 mg. of 3:20-bisethylenedioxy-1β:11α-oxido-5α-pregnane are suspended in 8 ml. of methanol and, after the addition of 0.02 ml. of concentrated sulfuric acid, allowed to stand at 20° C. for 15 minutes. The mixture is shaken from time to time. The solution is then neutralized with saturated sodium bicarbonate solution, extracted with ether, the ethereal layer washed nuetral with water, dried and evaporated. For complete cleavage of the C–20 ketal, the resulting crude product is dissolved in 2 ml. of glacial acetic acid, treated with 0.5 ml. of water, and heated to 60° C. for 10 minutes. The subsequent working up yields 245 mg. of the methyl ester of 2:3-seco-Δ^1-11α-hydroxy-20-oxo-5α-pregnene-3-acid. After being recrystallized from a mixture of ether and petroleum ether, the compound melts at 110° C. (The IR spectrum exhibits bands at 2.81μ, 5.78μ, 5.90μ, 6.5μ, 7.23μ, 7.30μ, 7.36μ, 8.15μ, 8.40μ, 8.55μ, 8.65μ and 10.80μ.) Optical rotation $[\alpha]_D^{27} = +77.3° \pm 1°$ (c.=0.818 in chloroform). The same compound is obtainable also from the glycol ester described in Example 12 by hydrolysis to form 2:3-seco-Δ^1-11α-hydroxy-20-oxo-5α-pregnene-3-acid and subsequent esterification by means of diazomethane.

By ozonization of the methyl ester in glacial acetic acid solution at room temperature and subsequent after-oxidation with chromium-(VI)-oxide+sulfuric acid in acetone there is obtained in good yield the 1:11-lactone of the 3-methyl ester of 2:3-seco-2-nor-11α-hydroxy-20-oxo-5α-pregnane-1:3-diacid. The compound melts at 209–210° C. after being recrystallized three times from a mixture of methylene chloride and hexane. Optical rotation $[\alpha]_D^{25} = +45.9 \pm 1°$ (c.=0.980 in chloroform).

Example 14

200 mg. of Δ^5 - 3 - ethylenedioxy-1ξ:11-α-oxido-17β-acetoxy-17α-methyl-androstene, dissolved in 30 ml. of absolute tetrahydrofuran, are added dropwise with stirring

and cooling to a suspension of 120 mg. of lithium aluminum hydride in 25 ml. of tetrahydrofuran. The reaction mixture is then refluxed for 2 hours with stirring, and worked up as usual. There is obtained the crude Δ^5-3-ethylenedioxy-1ξ:11α-oxido-17β-hydroxy - 17α - methyl-androstene.

Example 15

150 ml. of absolute benzene, 1.50 grams of dried calcium carbonate and 5.0 grams of lead-IV-acetate freed from excess acetic acid in vacuo are boiled for a short time; 1.00 gram of Δ^5-3-ethylenedioxy-11α-hydroxy-17β-acetoxy-17α-methyl-19-nor - androstene (prepared from 11α - hydroxy-19-nor-methyltestosterone) is then added and the whole boiled under reflux for 18 hours with stirring. The reaction solution which still contains excess lead-IV-acetate is filtered off from the inorganic portion and worked up as described in the preceding examples. 1.25 grams of crude cyclisation mixture are obtained which contains in addition the oily reaction product of the solvent. By chromatography on aluminum oxide there is obtained in 35% yield purse Δ^5-3-ethylenedoxy-1α:11α-oxdo-17β-acetoxy-17α - methyl-19-nor-androstene whose bands in the infrared and nuclear resonance spectra correspond to the expected as regards position and intensity.

Example 16

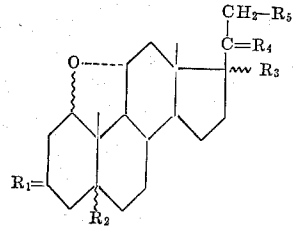
200 mg. of Δ^5 - 3 - ethylenedioxy-1α:11α-oxido-17β-acetoxy-17α-methyl-19-nor-androstene dissolved in 50 ml. of absolute tetrahydrofuran are added dropwise with cooling to a stirred suspension of 200 mg. of lithium aluminum hydride in 95 ml. of tetrahydrofuran. When the addition is complete, cooling is replaced by an oil bath and the reaction mixture boiled under reflux for 1 hour with stirring. Working up in the customary manner yields 157 mg. of Δ^5-3-ethylenedioxy-1α:11α-oxido-17β-hydroxy-17α-methyl-19 - nor - androstene which may be subjected to hydrolysis either after recrystallization or directly.

By heating Δ^5 - 3 - ethylenedioxy-1α:11α-oxido-17β-hydroxy-17α-methyl-19-nor-androstene for a short time (5 minutes) at 60° C. with acetic acid of 66% strength and by subsequent working up there is obtained Δ^5-3-oxo-1α:11α-oxido-17β-hydroxy-17α-methyl - 19 - nor - androstene.

Subsequent treatment with a mixture of glacial acetic acid and sodium acetate under normal conditions leads to the splitting of the ether ring with simultaneous aromatisation of ring A and formation of $\Delta^{1:3:5:10}$-3:11α:17β-trihydroxy-17α-methyl-oestratriene which may be characterized by its infrared, ultaviolet and nuclear magnetic resonance spectra.

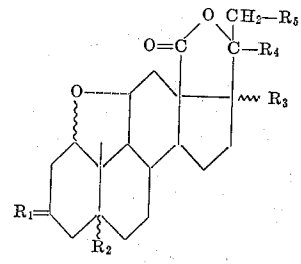
What is claimed is:

1. A compound of the formula



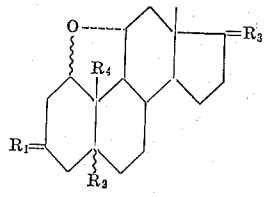
in which R_1 is a member selected from the group consisting of oxo, lower alkylenedioxy, hydrogen and hydroxy and hydrogen and acyloxy, R_2 is a member selected from the group consisting of an α-positioned hydrogen and a β-positioned hydrogen, each of R_3 and R_5 is a member selected from the group consisting of hydroxy and acyloxy and R_4 is a member selected from the group consisting of oxo and lower alkylenedioxy, said acyloxy radicals being derived from acids selected from the group consisting of lower aliphatic, monocyclic cycloaliphatic, monocyclic carbocyclic aryl-lower aliphatic, monocyclic carbocyclic aromatic, monocyclic heterocycli aromatic mono- and dicarboxylic acids, lower alkane and monocyclic carbocyclic aromatic sulfonic acids.

2. A member selected from the group of a compound of the formula



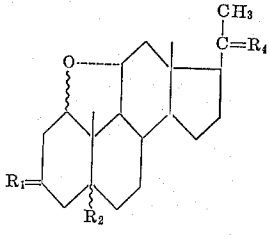
in which R_1 is a member selected from the group consisting of oxo, lower alkylenedioxy, hydrogen and hydroxy and hydrogen and acyloxy, R_2 is a member selected from the group consisting of an α-positioned hydrogen and a β-positioned hydrogen, each of R_3 and R_5 is a member selected from the group consisting of hydrogen, hydroxy and acyloxy and R_4 is a member selected from the group of hydroxy and acyloxy, and the dehydro compound thereof containing a double bond extending from carbon atom 5, said acyloxy radicals being derived from acids selected from the group consisting of lower aliphatic, monocyclic cycloaliphatic, monocyclic carbocyclic aryl-lower aliphatic, monocyclic carbocyclic aromatic, monocyclic heterocyclic aromatic mono- and dicarboxylic acids, lower alkane and monocyclic carbocyclic aromatic sulfonic acids.

3. A member selected from the group of a compound of the formula



in which R_1 is a member selected from the group consisting of oxo, lower alkylenedioxy, hydrogen and hydroxy and hydrogen and acyloxy, R_2 is a member selected from the group consisting of an α-positioned hydrogen and a β-positioned hydrogen, R_3 is a member selected from the group of oxo, lower alkylenedioxy, hydrogen and β-hydroxy, hydrogen and β-acyloxy, methyl and β-hydroxy and methyl and β-acyloxy and R_4 is a member selected from the group consisting of hydrogen and methyl, and the dehydro compound thereof containing a double bond extending from carbon atom 5, said acyloxy radicals being derived from acids selected from the group consisting of lower aliphatic, monocyclic cycloaliphatic, monocyclic carbocyclic aryl-lower aliphatic, monocyclic carbocyclic aromatic, monocyclic heterocyclic aromatic mono- and dicarboxylic acids, lower alkane and monocyclic carbocyclic sulfonic acids.

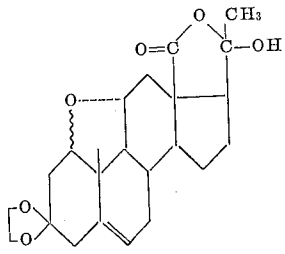
4. A compound of the formula



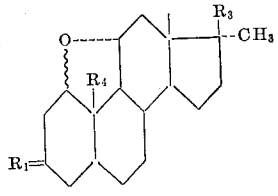
in which each of R_1 and R_4 is a member selected from the group consisting of oxo and ethylenedioxy and R_2

is a member selected from the group of an α-positioned hydrogen and a β-positioned hydrogen.

5. A compound of the formula

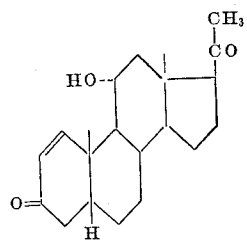


6. A compound of the formula



in which R_1 is a member selected from the group consisting of oxo and ethylenedioxy, R_3 is a member selected from the group consisting of hydroxy and acetoxy and R_4 is a member selected from the group consisting of hydrogen and methyl.

7. A member selected from the group consisting of a compound of the formula



and the 5-dehydro compound thereof.

8. 3β-acetoxy-1ξ:11α-oxido-5α-spirostane.

9. 3β-acetoxy-1ξ:11α-oxido-5α-cholestane.

10. 3:20-bisethylenedioxy-1:11α-oxido - 21 - acetoxy-5β-pregnane.

11. A 18:20-lactone of a $\Delta^{1:5}$-3-oxo-11α:20-dihydroxy-pregnadiene-18-acid.

12. $\Delta^{1:5}$-3-oxo-11α-hydroxy-17β-acetoxy-17α - methyl-androstadiene.

13. 2:3-seco-Δ^1-11α-hydroxy-20-oxo-pregnene-3-acid.

14. Glycol ester of 2:3 - seco-Δ^1-11α-hydroxy-20-oxo-pregnene-3-acid.

15. Glycol ester of 2:3-seco-11α-hydroxy-20-oxo-5α-pregnane-3-acid.

16. Δ^4-3:20-dioxo-9:11-seco-11-nor-pregnene.

17. 18:20 - lactone of Δ^4-3-oxo-9:11-seco-11-nor-20β-hydroxy-pregnene-18-acid.

18. 1:11-lactone of 3-methyl ester of 2:3-seco-2-nor-11α-hydroxy-20-oxo-5α-pregnane-1:3-diacid.

References Cited by the Examiner

Kalvoda et al.: Helv. Chim. Acta 44, 186–198 (Feb. 1, 1961).

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UNITED STATES PATENT OFFICE

CERTIFICATE OF CORRECTION

April 25, 1967

Patent No. 3,316,253

Albert Wettstein 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 10, line 61, before "sulfonic" insert -- aromatic --.

Signed and sealed this 28th day of November 1967.

(SEAL)
Attest:

Edward M. Fletcher, Jr.
Attesting Officer

EDWARD J. BRENNER
Commissioner of Patents