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Schülze et al.

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[54] DEPOT STEROID ESTERS

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[30] **Foreign Application Priority Data**

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[51] **Int. Cl.**[2] **C07J 21/00**

[52] **U.S. Cl.** ..... **260/239.55 C**; 260/397.4; 260/397.45; 260/397.5

[58] **Field of Search** 260/397.45, 397.4, 397.5

[56] **References Cited**

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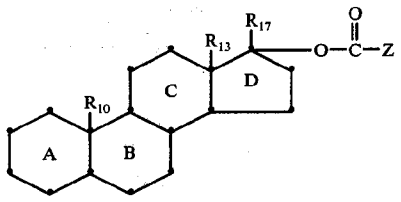
Primary Examiner—Elbert L. Roberts
Attorney, Agent, or Firm—Millen & White

[57] **ABSTRACT**

Steroid esters of the Formula I



I

wherein the A, B, C, and D rings can be substituted in the usual manner,

R_{10} is hydrogen or methyl;

R_{13} is alkyl of 1–3 carbon atoms;

R_{17} is 17α-alkynyl or alkadiinyl of up to 4 carbon atoms or 17β-acetyl,

Z is X—OH, Y—CO—OH, X—O—CO—Y—CO—OH, X—O—CO—R, Y—CO—OR, X—O—CO—Y—CO—OR, or X—O—SO_2—R;

X is a straight-chain or branched alkylene of 1–6 carbon atoms, optionally interrupted by O or S atoms, wherein the chain or branches can be substituted by —OH, —O—CO—R, or —O—SO_2—R;

Y is a direct bond, a straight-chain or branched carbon chain of 1–3 atoms, optionally interrupted by an O or S atom if Y is linked to the steroid residue via —O—CO—; of 1–16 atoms if Y is linked to X via —O—CO; or 1,4-phenylene, 1,4-cyclohexylene, or 1,3-cyclopentylene optionally substituted by alkyl of 1–2 carbon atoms, or groups analogously 1,2- and 1,3-disubstituted, respectively; and

R is an optionally substituted alkyl of up to 22 carbon atoms, have longer acting activity than the corresponding unesterified steroids and higher activity than the corresponding long chain esters.

37 Claims, No Drawings

DEPOT STEROID ESTERS

BACKGROUND OF THE INVENTION

It is known that protracted effectiveness can be achieved by esterifying biologically active steroid alcohols with long-chain, branched, or cyclic fatty acids and/or by converting biologically active lower esters of steroid alcohols into higher esters.

The chain length or the branching of the fatty acid is the factor governing the desired protracting effect. It is possible, for example, to obtain considerable protracting effect with an undecylate, but a considerable decrease in effectiveness must be tolerated as a consequence of greatly diminished cleavage of the steroid ester liberated from the depot. Since saponification of a tertiary ester takes place very gradually compared to metabolism or direct excretion of the ester, physiologically undesirably high doses of the long-chain ester must be administered to attain the therapeutic effect of the alcohol.

It has now been found that the depot steroid esters of this invention are either completely or almost completely saponified, yielding correspondingly high levels of activity and that the saponification rate and thus the period of activity can be controlled by the selection of X, Y and R of Formulae I, II, and III.

SUMMARY OF THE INVENTION

In a compositional aspect, this invention relates to a depot steroidal ester of the cyclopentanopolyhydrophenanthrene series having at the 13-position an alkyl of 1–3 carbon atoms; at the 10-position H or methyl; and at the 17-position (a) a 17α-alkynyl or alkadiinyl of up to 4 carbon atoms or (b) a 17β-acetyl and, in the opposition configuration,

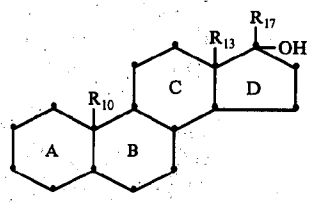
wherein

Z is alkenyl of up to 4 carbon atoms, X-OH, Y-CO-OH, X-O-CO-Y-CO-OH, X-O-CO-R, Y-CO-OR, X-O-CO-Y-CO-Or, or X-O-SO_2-R, and X is a straight-chain or branched alkylene, oxalkylene or thiaalkylene of 1–6 carbon atoms, unsubstituted or substituted by an —OH, —O-CO-R, or —O-SO_2-R;

Y is a direct bond, a straight-chain or branched alkylene, oxaalkylene or thiaalkylene of 1–3 carbon atoms when Y is linked at the 17-position of the steroid residue via -O-CO-; alkylene, oxaalkylene or thiaalkylene of 1–16 carbon atoms, unsubstituted or substituted by an -OH, -OCOR, or -OSO_2R when Y is linked to X via —O-CO-; or 1,4-phenylene, 1,4-cyclohexylene, or 1,3-cyclopentylene substituted by up to two alkyl of 1–2 carbon atoms, and R is alkyl or oxaalkyl of up to 22 carbon atoms.

In another compositional aspect, this invention relates to a pharmaceutical composition, comprising a depot steroidal ester, as above, in admixture with a pharmaceutically acceptable carrier.

This invention also relates to a process for the production of the novel depot esters, by conventionally esterifying steroid alcohols of the formula



wherein the A, B, C, and D rings can be substituted in the usual manner and R_{10}, R_{13}, and R_{17} are as above.

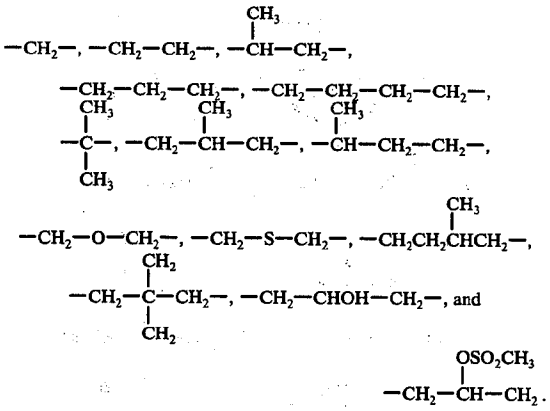
DETAILED DESCRIPTION

The steroid molecule can be further substituted by the usual substituents, examples of which include: etherified or esterified hydroxy in the α- or β-configuration at the 1-, 2-, 3-, 4-, 7-, 11-, 15- and/or 16-position; keto in the 3-, 6- and/or 11-position; saturated or unsaturated alkyl of 1–5 carbon atoms, preferably methyl or ethyl, in the 1-, 2-, 4-, 6-, 7- and/or 16-position; methylene in the 1,2-, 6,7- and/or 15,16-position; halogen, preferably fluorine or chlorine, in the 2-, 4-, 6-, 7-, 9-, 11- and/or 16-position.

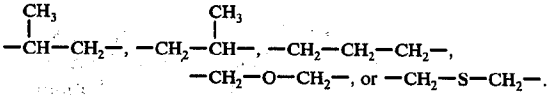
The A, B, C, and D rings can be saturated or unsaturated, that is, double bonds can be present, for example, in the 1(2)-, 3(4)-, 4(5)-, 5(10)-, 5(6)-, 6(7)-, 9(10)-, 9(11)-, 11(12)- and/or 15(16)-positions.

R_{17} alkynyl includes ethynyl, chloroethynyl, propynyl, and butadiynyl, of which ethynyl is preferred.

X is straight-chain or branched alkylene of 1–6 carbon atoms, optionally interrupted by O or S atoms. The branched groups as well as the end groups of X can be substituted by —OH, —O-CO-R, or -O-SO_2-R. For example, X can be:



Y is a direct carbon-carbon bond, a straight or branched carbon chain of 1–3 atoms, optionally interrupted by an O or S atom, for example —CH_2-, -CH_2-CH_2-,

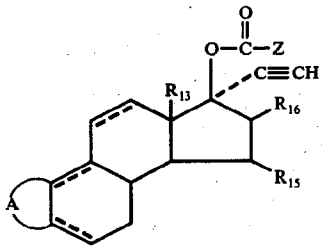


Also, Y can be 1,4-phenylene, 1,4-cyclohexylene, or 1,3-cyclopentylene group, optionally substituted by alkyl of 1–2 carbon atoms. If Y is linked to X by -O-CO-, Y can also be a carbon chain of 1–16 atoms, optionally interrupted by one or more O or S atoms.

R is an univalent hydrocarbon residue of the aliphatic, cycloaliphatic, aromatic, aromatic-aliphatic, or heterocyclic series. The hydrocarbon residue can be saturated, unsaturated, and/or substituted, for example, by alkoxy, oxo, amino, and halogen atoms. R can be of up to 22 carbon atoms, preferably 4–18 carbon atoms.

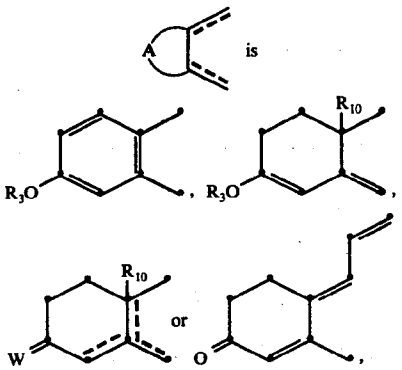
Examples of R and contemplated equivalents include, but are not limited to: alkyl, and substituted alkyl, e.g., methyl, diethylaminomethyl, chloromethyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.-butyl, pentyl, isopentyl, tert.-pentyl, 2-methylbutyl, hexyl, heptyl, octyl, nonyl, decyl, dodecyl, pentadecyl, hexadecyl, and octadecyl; cycloalkyl, e.g., cyclopentyl, cyclohexyl, and cyclopentylmethyl; aryl, e.g., phenyl, benzyl, 2-phenethyl, tolyl, cinnamyl, α- and β-naphthyl; heterocyclic groups, e.g., pyridyl, piperidyl, pyrrolidinyl, furanyl, piperidinomethyl, and morpholinomethyl; and hydrocarbon groups interrupted by oxygen, e.g., 3,6,9-trioxaisoundecane.

Preferred depot steroid esters are compounds of Formula II



II

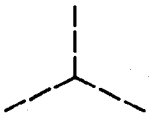
wherein R_{13} and Z are as in Formula I; the dashed lines are optional, double carbon-carbon bonds;



R_{10} is hydrogen or methyl;

R_3 is hydrogen, lower alkanoyl, alkylsulfonyl, alkyl, or cycloalkyl;

W is H_2, O, or H,OR_3;

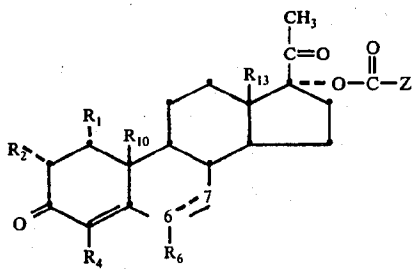


is a double bond in the 4,5-, 5,6-, or 5,10- position; and

R_{15} and R_{16} each are hydrogen or collectively are methylene in the α- or β-position or an additional carbon-carbon bond between the C_{15} and C_{16} carbon atoms.

Preferred lower alkanoyl R_3 are acetyl, propionyl, and butyryl. Alkyl or alkyl in alkylsulfonyl are likewise of 1–4 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, and tert.-butyl. Cycloalkyl are of 3–8 carbon atoms, of which cyclopentyl is preferred.

Other preferred depot steroid esters are compounds of Formula III



III

wherein R_{10}, R_{13}, and Z are as in Formula I,

R_1 and R_2 each are hydrogen or collectively are methylene or a further carbon-carbon bond between the C_1 and C_2 carbon atoms,

R_4 is hydrogen or chlorine,

R_6 is hydrogen, chlorine or methyl, and

6–7 is a single or double bond between the C_6 and C_7 carbon atoms.

Included within the compounds of the invention are compounds of Formula I, wherein:

(a) R_{17} is 17α-alkynyl;

(b) R_{17} is 17β-acetyl;

(c) Z is alkenyl of up to 4 carbon atoms, including (a)–(b);

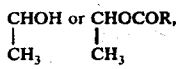
(d) Z is CH_2OH, or CH_2OCOR, including (a)–(b);

(e) Z is CH_2CH_2OH or CH_2CH_2OCOR, including (a)–(b);

(f) Z is CH_2COOH, or CH_2COOR, including (a)–(b);

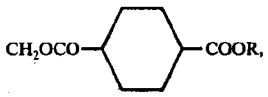
(g) Z is COOH or COOR, including (a)–(b);

(h) Z is



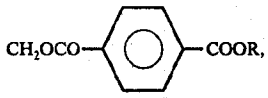
including (a)–(b);

(i) Z is



including (a)–(b);

(j) Z is

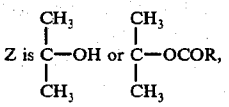


including (a)–(b);

(k) Z is CH_2OSO_2R, including (a)–(b);

(l) Z is $CH_2CH_2CH_2OCOR$, including (a)–(b);

(m)



including (a)–(b);

(n) R is oxaalkyl of up to 22 carbon atoms including (a)–(m);

(o) R is alkyl of up to 22 carbon including (a)–(m).

Also, within the compounds of this invention are 17α- or 17β-thioesters, e.g., 17-carbomethoxy-thioacetoxy and methoxycarbonyl-methylthioacetoxy steroids.

The depot steroid esters of this invention have higher levels of effectiveness than steroid esters known heretofore. The increase in effectiveness is up to 800%. The novel steroid esters have the same pharmacological properties as conventional, corresponding steroid alcohols from which they are produced, but have particularly strong estrogenic and/or progestational activities.

Whereas usually, following esterification of the tertiary 17-hydroxy group during in vitro experiments, there is no longer a receptor linking to the steroid, a receptor linkage is present in the 17-hydroxy esters (Z is X-OH) of this invention, e.g., in case of the 17-glycolates, which is diminished in receptor linking merely by a factor of 3–4 with respect to the steroid alcohol. Thus, the desired therapeutic effect is even enhanced, because pharmacologically effective compounds are already present even before cleavage of the hydroxy esters.

The novel tertiary depot esters are produced by esterification with a short-chain hydroxy- or carboxycarboxylic acid, HO-X-COOH or HOOC-Y-COOH, respectively, and optionally further esterification of an initially obtained hydroxy- or carboxy- carboxylic acid ester with another carboxylic acid (R-COOH), dicarboxylic acid (HOOC-Y-COOH), sulfonic acid (R-SO_2OH) and/or an alcohol (R-OH), or by esterification with the desired acylated hydroxycarboxylic acid and-/or or mono-esterified carboxycarboxylic acid. In this way, compounds having one, two, or three esters groups are obtained.

The length and structure, especially of the second and optionally third ester group, determine the duration of activity. By esterification with hydroxy- and carboxycarboxylic acids, fat solubility of the steroid is increased and, in many cases, the melting point is simultaneously raised. Consequently, several of the novel depot esters can be administered intramuscularly in an oily solution as well as in an aqueous microcrystal suspension.

Esterification of the 17α-hydroxy is carried out by methods generally known to those skilled in the art. The steroid alcohol can be dissolved in an inert solvent and reacted with the desired acid anhydride or halide in the presence of an acidic or alkaline catalyst at temperatures of 0°–150° C.

A steroid alcohol can be reacted with a free hydroxycarboxylic acid or a hydroxycarboxylic acid esterified on the hydroxy group, or with a free or mono-esterified dicarboxylic acid by treatment with trifluoroacetic anhydride in an inert solvent, optionally with addition of an acidic catalyst, at temperatures between about 0° C. and 40° C.

Examples of acidic catalysts are p-toluenesulfonic acid, perchloric acid and sulfuric acid. Basic catalysts, which can also serve as the solvent, are, for example, triethylamine, pyridine, and collidine.

Any inert solvent can serve as reaction medium, but benzene or aromatic solvents, such as toluene or chlorobenzene, are preferred, along with ethers, such as diethyl ether, dioxane or tetrahydrofuran; hydrocarbons, such as hexane; halogenated hydrocarbons, such as methylene chloride, ethylene chloride or chloroform; and polar solvents; e.g., acetonitrile and dimethyl sulfoxide.

A hydroxy ester (X-OH) obtained from a hydroxy fatty acid can be esterified on the free hydroxy group in the customary manner. Esterification agents are preferably acid anhydrides or halides, in the presence of a basic catalyst. Reaction temperatures are about 0°–100° C. The hydroxy fatty acids can contain 1–3 hydroxy groups, preferably 1 hydroxy group.

An acyloxy fatty acid ester (Z is X-O-CO-R) obtained from an acyloxy fatty acid can be saponified with a catalytic amount of an solution of an alkali metal or alkaline earth metal hydroxide in alcohol at temperatures between about 0° and 50° C. and reactions times of 1 minutes to 3 hours.

The reaction mixture can also contain inert solvents and diluents, such as methylene chloride, diethyl ether, and tetrahydrofuran. If desired, esterification can be carried out in a second step after saponification with the desired carboxylic or sulfonic acid (R-COOH or R-SO_2OH) or dicarboxylic acid (HOOC-Y-COOH).

The optional esterification of a free carboxy group of an initially formed mono-ester (Y-CO-OH) takes place likewise according to conventional methods. Thus, a mono-ester can be reacted, for example, with diazomethane or diazoethane, to obtain the corresponding methyl or ethyl ester. A generally applicable method is reaction of a mono-ester with an alcohol in the presence of carbonyl diimidazole, dicyclohexylcarbodiimide, or trifluoroacetic anhydride. It is also possible to convert an acid to a silver salt and react the latter with a R-halogenide. A further method is in conversion of a mono-ester with a free carboxyl group to the corresponding alkyl ester by an intermediate corresponding dimethylformamide alkyl acetal.

A mono-ester can be reacted in the presence of a strongly acidic catalyst, such as hydrogen chloride, sulfuric acid, perchloric acid, trimethylsulfonic acid, or p-toluenesulfonic acid with an alcohol or a lower alkanecarboxylic acid ester of an alcohol. The carboxy of a mono-ester can be converted to an acid chloride or anhydride and then reacted with an alcohol in the presence of a basic catalyst.

It is frequently advantageous first to prepare, in a single step, a hydroxy or carboxy ester, respectively, esterified with a lower fatty acid or with a lower alcohol; to saponify this product to a free hydroxy or carboxy ester; and, as a final step, carry out esterification with an acid or an alcohol of the desired chain length.

The 17-glycolic acid esters can be prepared as follows:

(1) A 17-crotonic acid ester is prepared using crotonic acid in the presence of trifluoroacetic anhydride.

(2) After blocking any keto groups which are present, for example, in the 3- or 3,20-positions, preferably by ketalization, an oxidation is conducted with potassium permanganate in the presence of formic acid at temperatures around the freezing point, to obtain a 2,3-dihydroxybutyric acid ester.

(3) By oxidative cleavage with periodate at temperatures between about 0° and 50° C., a 17-glyoxylic acid ester, which is converted into the desired glycolic acid ester during the reduction, is obtained.

Oxidation with permanganate and oxidative splitting with periodate are conducted in aqueous, inert solvent, such as, for example, acetone, tetrahydrofurna, and dioxane. The reduction can be effected in the usual manner with alkali metal boranate or lithium tri-tert.-butoxyalanate. Depending on the final product desired, any blocked keto groups present are liberated directly or after first esterifying a hydroxy group of the glycolic acid ester.

The invention also concerns pharmaceutical preparations, especially depot preparations, of the steroid esters of Formula I.

The progestationally and/or estrogenically active steroid esters are suitable, for example, for fertility control in humans and animals or for the treatment of climacteric complaints in women. Also combinations of, for example, progestational and estrogenic, or estrogenic and androgenic steroid esters are possible.

The effective dose depends on the purpose of the treatment, on the type of active agent, and on the desired duration of effectiveness. The effective dose of, for example, 17α-ethynyl-18-methyl-17β-(O-undecanoylglycoloyoxy)-4-estren-3-one for fertility control in the human female is approximately 10–50 mg. for three months. The amount of other, progestationally active, steroid esters administered is equal to that corresponding to 10–50 mg. of 17α-ethynyl-18-methyl-17β-(O-undecanoylglycoloyloxy)-4-estren-3-one each three months.

The preparations are injected intramuscularly in an oily solution or in an aqueous crystalline suspension. The injection volume is about 1–4 ml., preferably 1–2 ml.

To produce the oily solution, the steroid esters are dissolved in an oily sovlent or solvent mixture suitable for the injection, filtered under sterile conditions, and charged into ampoules under aseptic conditions.

Examples of preferred oily solvents are sesame oil and castor oil. To increase the solubility of the active agent, it is possible to add solubilizers, for example, benzyl benzoate or benzyl alcohol, to the oily solvents.

Other vegetable oils which can be utilized include, e.g, linseed oil, cottonseed oil, sunflower oil, peanut oil, olive oil, and wheat-germ oil.

Synthetic oils, such as polyethylene glycol, triglycerides of higher saturated fatty acids and mono-esters of higher fatty acids are also useable.

A mixture of castor oil/benzyl benzoate in a ratio of 6:4 is a preferred solvent mixture.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative and not limitative of the remainder of the disclosure in any way whatsoever. The temperature in the following examples is indicated in degrees Celsius.

EXAMPLE 1

30.9 g. of crotonic acid is combined in 800 ml. of benzene with 48.1 ml. of trifluoroacetic anhydride and stirred for 30 minutes at room temperature. Then, 50 g. of 17α-ethynyl-17β-hydroxy-18-methyl-4-estren-3-one is added thereto and the mixture agitated for 30 minutes at room temperature. The reaction solution is diluted with ether, washed with water and sodium bicarbonate solution, dried, and evaporated. The residue is taken up in 1.3 l. of methanol for enol ester cleavage, combined with 130 ml. of 8 vol.-% sulfuric acid, and heated under reflux for 2 hours. After precipitation in ice water, the precipitate is filtered off, washed with water, taken up in methylene chloride, and dried. The residue obtained after evaporation is recrystallized from diisopropyl ether-acetone, thus obtaining 43.3 g. of 17α-ethynyl-17β-crotonoyloxy-18-methyl-4-estren-3-one, m.p. 187°–188°.

UV: $\epsilon_{211} = 18{,}700$; $\epsilon_{238} = 18{,}100$.

45 g. of 17α-ethynyl-17β-crotonoyloxy-18-methyl-4-estren-3-one is combined in 450 ml. of methylene chloride with 90 ml. of triethyl orthoformate, 112 g. of 2,2-dimethyl-1,3-propanediol, and 450 mg. of p-toluenesulfonic acid and agitated for 60 minutes at a bath temperature of 50°. The mixture is then diluted with ether, washed with sodium bicarbonate solution and water, dried, and evaporated. The residue is chromatographed on silica gel, thus producing 39.5 g. of 17α-ethynyl-17β-crotonoyloxy-3,3-(2,2-dimethyltrimethylenedioxy)-18-methyl-5- and -5(10)-estrene in the form of an oil.

40 g. of 17α-ethynyl-17β-crotonoyloxy-3,3-(2,2-dimethyltrimethylenedioxy)-18-methyl-5- and -5(10)-estrene is dissolved in 1.5 l. of acetone, cooled in an ice bath, and then 11.2 ml. of 100% formic acid is added to the reaction mixture. Within 2 hours, a solution of 23.7 g. of potassium permanganate in 395 ml. of water and 3.3 l. of acetone is also added to the mixture, whereafter the latter is agitated for 30 minutes at 0°. One liter of methylene chloride is added, and the mixture is filtered off from the thus-separated manganese dioxide. The filtrate is extensively concentrated under vacuum; the residue is taken up in ether, washed with water, dried, and evaporated. After chromatography on silica gel, the product is, in addition to 12 g. of unreacted starting material, 30.2 g. of 17α-ethynyl-17β-(2,2-dihydroxybutyryloxy)-3,3-(2,2-dimethyltrimethylenedioxy)-18-methyl-5- and -5(10)-estrene as an oil.

30 g. of 17α-ethynyl-17β-(2,2-dihydroxybutyryloxy)-3,3-(2,2-demethyltrimethylenedioxy)-18-methyl-5- and -5(10)-estrene is combined in 1.5 l. of dioxane with 89.6 g. of sodium periodate in 450 ml. of water; the mixture is then stirred for 1 hour at room temperature, stirred into ice water, extracted with methylene chloride, washed with water, and dried. After evaporation, the product is 28.5 g. of crude 17α-ethynyl-3,3-(2,2-dimethyltrimethylenedioxy)-17β-glyoxoyloxy-18-methyl-5- and -5(10)-estrene.

32.5 g. of crude 17α-ethynyl-3,3-(2,2-dimethyltrimethylenedioxy)-17β-glyoxoyloxy-18-methyl-5- and -5(10)-estrene is combined in 995 ml. of methanol and 142.5 ml. of water under ice cooling with incremental portions of 6.5 g. of sodium boranate. The mixture is then agitated for 10 minutes at the ice bath temperature and stirred into ice water. The precipitate-containing phase, acidified with 2N sulfuric acid, is extracted with ether, washed with water, and dried. The residue obtained after evaporation is chromatographed on silica gel, thus obtaining 30.5 g. of 17α-ethynyl-3,3-(2,2-dimethyltrimethylenedioxy)-17β-glycoloyloxy-18-methyl-5- and -5(10)-estrene. A sample recrystallized from diisopropyl ether melts at 215.5°–219°.

200 mg. of 17α-ethynyl-3,3-(2,2-dimethyltrimethylenedioxy)-17β-glycoloyloxy-18-methyl-5- and -5(10)-estrene is allowed to stand in 2 ml. of pyridine

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Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

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Sync your system to PACER to automate legal marketing.