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PHARMACEUTICALLY ACTIVE DERIVATIVES OF ETHANOOCTAHYDROPHENANTHRENE

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U.S. Cl. 260—473 8 Claims

ABSTRACT OF THE DISCLOSURE

This invention teaches that novel disubstituted and polysubstituted derivatives of 2,4′ - ethanooctahydrophenanthrene are useful as antifertility agents when administered to animals.

BACKGROUND OF THE INVENTION

This invention relates to di and polysubstituted derivatives of 2,4′-ethanooctahydrophenanthrene. It has been discovered that the subject compounds surprisingly are effective for preventing pregnancy.

This activity for the subject compounds is all the more startling when these compounds are compared in structure to contraceptive agents presently known to the medical art.

There are, at present, antifertility agents known to the medical arts. The most widely accepted, orally effective, antifertility agents are mixtures of steroidal estrogens and progestins. When these agents are administered, a pseudopregnant condition is established and ovulation is prevented. In order to induce this pseudopregnant condition, these agents are administered orally for about twenty days of the menstrual cycle. Although they are quite effective, this dosage regimen can result in side effects. The most commonly occurring side effects are similar to the symptoms observed during pregnancy. These side effects include nausea, occasional vomiting, dizziness, headache, breast enlargement and pigmentation of the nipples, particularly during the first cycle in which these agents are administered.

The fact that these agents require a cyclic administration regimen also presents a problem. They must be administered without fail each day of the 20-day period or there is danger of breakthrough bleeding or lack of efficacy.

Whereas the estrogen-progestin mixtures now most widely used for the prevention of pregnancy must be taken for relatively long periods in anticipation of coitus in regular cycles, the compounds of this invention can be administered after coitus to prevent pregnancy. Although the exact mechanism of action is not well understood, animal tests indicate that nidation is in some manner prevented.

Therefore, in addition to the striking structural difference of the compounds of this invention over known contraceptive agents, it also appears that the compounds of this invention exhibit a mechanism of action that materially differs from presently employed contraceptive drugs.

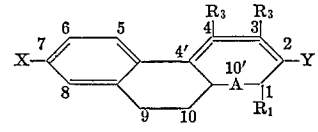
This new mechanism of action has numerous practical advantages such as ease of use, elimination of protracted periods of administration, elimination of a scheduled regimen of medication, and the avoidance of a continual state of pseudopregnancy, which is responsible for many side effects.

SUMMARY OF THE INVENTION

In summary, this invention relates to novel di and polysubstituted derivatives of 2,4′ - ethanooctahydrophenanthrene, the method of using said compounds as antifertility agents and pharmaceutical compositions containing said compounds as the active ingredient therein.

More particularly, this invention relates to compounds of the formula

(I)

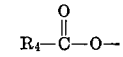


where:

A is a single or a double bond; and

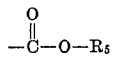
R_1, R_2, R_3 can be the same or different and can be H or alkyl of one through six carbons; and

X is H, HO, RO where R is an alkyl of one through four carbons, or

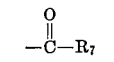


where R_4 is hydrogen or an alkyl of one through twelve carbons with the limitation that when X is hydrogen at least one of R_1, R_2, and R_3 must be alkyl of one through six carbons; and

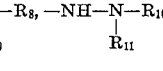
Y is



where R_5 is H, alkyl of one through six carbons, Me^+ where Me^+ is a non-toxic pharmaceutically acceptable salt-forming cation such as sodium, potassium, magnesium or ammonium, $—CH_2—OR_6$ where R_6 is hydrogen, an ester-forming monobasic acid radical such as acetyl, propionyl or an ester-forming dibasic acid radical, preferably forming hemi-esters such as hemisuccinyl, hemi-glutaryl or hemi-adipyl,



wherein R_7 is H, —NH—NH_2, —NHOH,



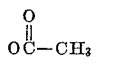
wherein R_8, R_9, R_{10} or R_{11} is the same or different and can be H, alkyl of 1–3 carbons, with the limitation that R_{10} and R_{11} can be taken together with the nitrogen to which they are bonded to form the following ring systems: pyrrolidino, piperidino or morpholino.

Preferred compounds of this invention are those compounds of Formula I in which A is a single bond or a double bond; X is HO—, H_3CO—, C_2H_5O—, or

CH_3CO_2—

Y is CH_2—OH, or —CO_2R_5 where R_5 is H—, CH_3—, C_2H_5—, sodium potassium, or ammonium; and at least one of R_1, R_2, R_3 is alkyl of one to two carbons.

Most preferred compounds of this invention are those compounds of Formula I where A is a single bond or a double bond; X is OH, OCH_3 or



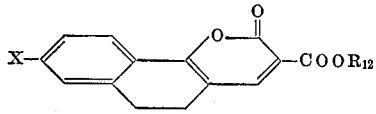
Y is COOH or CH_2OH; and each of R_1, R_2 and R_3 is H.

Another object of this invention is a method for preventing pregnancy in warm-blooded animals which comprises administering an effective amount of a compound of Formula I to the female animal.

This invention also relates to pharmaceutical compositions effective for use in preventing pregnancy when administered to warm-blooded animals. These compositions are comprised of the compounds of Formula I in combination with a pharmaceutically acceptable diluent.

This invention further relates to compounds useful as intermediates in the preparation of the compounds of Formula I above. These intermediates are represented by the following formulas:

(II)



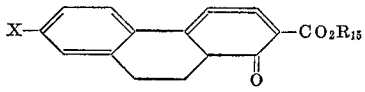
where:

R_{12} is alkyl of one through four carbons; and
X is $R_{13}O$— and $R_{14}CO_2$

where:

R_{13} is alkyl of one through four carbons and
R_{14} is hydrogen and alkyl of one through twelve carbons.

(III)



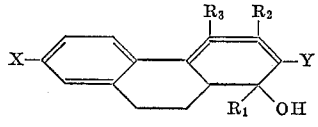
where:

R_{15} is alkyl of one through four carbons; and
X is $R_{16}O$— and $R_{17}CO_2$

where:

R_{16} is alkyl of one through four carbons and
R_{17} is hydrogen and alkyl of one through twelve carbons.

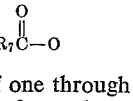
(IV)



where:

R_1, R_2, and R_3 can be the same or different and are selected from the group consisting of hydrogen and alkyl of one through six carbons;

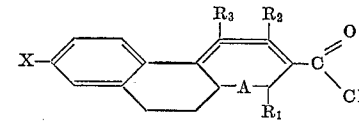
X is selected from the group consisting of hydrogen, HO, RO and



wherein R is an alkyl of one through four carbons and R_4 is hydrogen or alkyl of one through twelve carbons with the limitation that when X is hydrogen at least one of R_1, R_2 and R_3 is alkyl of one through six carbons; and

Y is $COOR_5$ where R_5 is hydrogen or alkyl of one through six carbons.

(V)



where:

A is a single bond or a double bond;

R_1, R_2 and R_3 can be the same or different and are selected from the group consisting of hydrogen and alkyl of one through six carbons;

X is selected from the group consisting of hydrogen, HO, RO and



wherein R is an alkyl of one through four carbons and R_4 is hydrogen or alkyl of one through twelve carbons with the limitation that when X is hydrogen at least one of R_1, R_2 and R_3 is alkyl of one through six carbons.

DESCRIPTION OF THE INVENTION

A convenient starting material for preparing the compounds of this invention is a substituted α-tetralone. The desired α-tetralone is treated with ethyl ethoxymethylenecyanoacetate in glyme in the presence of sodium ethoxide under a nitrogen atmosphere. The intermediate thus formed is treated with dilute aqueous hydrochloric acid to give an alpha pyrone such as 8-methoxy-5,6-dihydro-2-oxo - 2H - naphtho[1,2-b]pyran - 3 - carboxylic acid ethyl ester.

The α-pyrone is heated at 150–200° C. with ethylene under pressure (2,000–3,000 atm.) in the presence of a solvent such as benzene or without solvent to give the corresponding 2,3,4,4',9,10-hexahydro - 2,4' - ethanophenanthrene-2 carboxylic acid ethyl ester. This ester is then hydrolyzed to give the corresponding 2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid.

In order to prepare the 3,4-alkyl substituted ethanophenanthrene, the above α-pyrone is heated at 150–200° C. with an appropriate monoalkyl or dialkyl ethylene under pressure (1,000–1,500 atm.) in the presence of a solvent such as benzene or without solvent to give 3,4,9,10-tetrahydro - 3,4 - dialkylphenanthrene - 2 - carboxylic acid ethyl ester. This diene is heated at 150–200° C. with ethylene under pressure (2,000–3,000 atm.) to give 2,3,4,4',9,10-hexahydro - 3,4 - dialkyl-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester. The order in which the dialkyl substituted ethylene and the ethylene are added to the pyrone may be reversed. When the dialkyl groups of ethylene are not identical or the geometry of the dialkyl substituted ethylene is either cis or trans, the resulting 3,4-dialkyl derivative may consist of several isomers. They can be separated by conventional techniques such as fractional crystallization, distillation or chromatography.

In order to prepare the 2-alkyl substituted derivative, and appropriate 2,3,4,4',9,10-hexahydro - 2,4' - ethanophenanthrene-2-carboxylic acid ethyl ester is treated with borane (BH_3) in tetrahydrofuran (THF) or in ethylene glycol dimethyl ether (glyme). The resulting boron derivative is oxidized with chromic acid to give a keto-ester such as 1,2,3,4,4',9,10,10'-octahydro - 2,4' - ethano-1-oxophenanthrene-2-carboxylic acid ethyl ester. This keto-ester is reacted with appropriate alkyl Grignard reagent in THF to give the 2-alkyl substituted hydroxy-ester, which on treatment with p-toluenesulfonyl chloride in pyridine gives 2,3,4,4',9,10 - hexahydro - 1 - alkyl-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester. The appropriate keto-acid can be employed in this reaction in place of the keto-ester with equally satisfactory results.

When the corresponding 1,2,3,4,4',9,10,10'-octahydro

derivatives are desired, 2,3,4,4',9,10 - hexahydro - 2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester can be reduced in the presence of an hydrogenation catalyst such as platinum oxide and a solvent to give corresponding 1,2,3,4,4',9,10,10'-octahydro - 2,4' - ethanophenanthrene-2-carboxylic acid ethyl ester. Solvents which can be used for this reaction include ethanol, ethylacetate and glacial acetic acid.

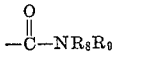
When the free carboxylic acid is desired, the 1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene - 2 - carboxylic acid ethyl ester is subjected to alkaline hydrolysis followed by acidification to give the free carboxylic acid.

A more convenient method of preparing the 1-alkyl-1,2,3,4,4',9,10,10'-octahydro derivative is to treat the above mentioned 1,2,3,4,4',9,10,10' - octahydro - 2,4' - ethano-1-oxophenanthrene - 2 - carboxylic acid ethyl ester with an appropriate alkyl Wittig reagent such as alkylene triphenyl phosphine or alkylene phosphonate in THF to give 1,2,3,4,4',9,10,10'-octahydro-2,4' - ethano - 1 - alkylenephenanthrene - 2 - carboxylic acid ethyl ester. This alkylene derivative is then reduced in the presence of a hydrogenation catalyst in a suitable solvent such as ethanol, ethyl acetate or glacial acetic acid to give corresponding 1,2,3,4,4',9,10,10'-octahydro - 2,4' - ethano - 1 - alkylphenanthrene - 2 - carboxylic acid ethyl ester.

The compounds of formula I in which Y is CH_2OH, hereinafter called the alcohols of this invention, are conveniently prepared by refluxing a mixture of the appropriate 1,2,3,4,4',9,10,10'-octahydro- or 2,3,4,4',9,10-hexahydro - 2,4' - ethanophenanthrene - 2 - carboxylic acid ethyl ester, a reducing agent preferably lithium aluminum hydride, and a solvent such as the THF or glyme under a nitrogen atmosphere until reaction is complete. The product is isolated by using conventional techniques.

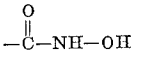
The compounds of Formula I in which Y is CHO, hereinafter called the carboxaldehydes of this invention, are prepared in the following manner. The appropriate 1,2,3,4,4',9,10,10' - octahydro- or 2,3,4,4',9,10 - hexahydro-2,4'-ethanophenanthrene - 2 - carboxylic acid is treated with thionyl chloride to give corresponding acyl chloride. The resulting acyl chloride is then reduced with lithium tri-t-butoxy aluminum hydride in THF or diglyme at −70° C. to give the corresponding carboxaldehyde.

The compounds of Formula I in which Y is



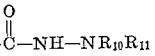
hereinafter called the carboxamides of this invention, are prepared by treating the appropriate carboxyl chloride prepared as above with aqueous solution of the appropriate amine resulting in the precipitation of the desired carboxamide.

The compounds of Formula I in which Y is



herein after called the hydroxamic acid of this invention, are prepared by treating a pyridine solution of appropriate carboxyl chloride with a solution of a hydroxylamine in pyridine. The resulting mixture is stirred for 15 to 25 hours and the desired carbohydroxamic acid is isolated and purified using conventional techniques.

The compounds of Formula I in which Y is



hereinafter called the carboxylic acid hydrazides of this invention, are conveniently prepared starting with the desired 1,2,3,4,4',9,10,10'-octahydro- or 2,3,4,4',9,10 - hexahydro - 2,4' - ethanophenanthrene - 2 - carboxylic acid lower alkyl ester in a suitable inert solvent such as amyl alcohol. The desired hydrazine is added to this solution and the resulting solution is refluxed for about 72 hours. The mixture is evaporated at reduced pressure and the hydrazide product in the residue is purified using conventional techniques.

Illustrative of the compounds of this invention are the following:

7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester
7-methoxy-1,2,3,4,4'-9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester
7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-hydroxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-hydroxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-hydroxy-2,3,4,4',9,10,10'-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-hydroxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-acetoxy-2,3,4,4',9,10,10'-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-acetoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-acetoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-acetoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-methoxy-1-methyl2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-methoxy-1-methyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-methoxy-1-methyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-methoxy-1-methyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-hydroxy-1-methyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-hydroxy-1-methyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-hydroxy-1-methyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-hydroxy-1-methyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-acetoxy-1-methyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-acetoxy-1-methyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-acetoxy-1-methyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-acetoxy-1-methyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
1-ethyl-7-methoxy-2,3,4,4'-9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
1-ethyl-7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
1-ethyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
1-ethyl-7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
1-ethyl-7-hydroxy-2,3,4,4',9,10,10'-hexahydro-2,4'-ethanophenanthrene-2-methanol
1-ethyl-7-hydroxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-acetoxy-1-ethyl-2,3,4,4',9,10,10'-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-acetoxy-1-ethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid

7-acetoxy-1-ethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-acetoxy-1-ethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
3,4-dimethyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
3,4-dimethyl-7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
3,4-dimethyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
3,4-dimethyl-7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
3,4-dimethyl-7-hydroxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
3,4-dimethyl-7-hydroxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
3,4-dimethyl-7-hydroxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
3,4-dimethyl-7-hydroxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-acetoxy-3,4-dimethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-acetoxy-3,4-dimethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-acetoxy-3,4-dimethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-acetoxy-3,4-dimethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-methoxy-1,3,4-trimethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-methoxy-1,3,4-trimethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-methoxy-1,3,4-trimethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-methoxy-1,3,4-trimethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-hydroxy-1,3,4-trimethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-hydroxy-1,3,4-trimethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-hydroxy-1,3,4-trimethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-hydroxy-1,3,4-trimethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-acetoxy-1,3,4-trimethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-acetoxy-1,3,4-trimethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-acetoxy-1,3,4-trimethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-acetoxy-1,3,4-trimethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-methoxy-1,3,4-triethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-methoxy-1,3,4-triethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid
7-methoxy-1,3,4-triethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol
7-methoxy-1,3,4-triethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol
7-ethoxy-3-ethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene carboxylic acid
7-ethoxy-4-ethyl-2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene carboxylic acid
1,3-dimethyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene carboxylic acid
1,4-dimethyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene carboxylic acid

As is evident from the foregoing, many of the compounds of this invention can exist in a number of isomeric forms. It is to be understood that where isomerism is possible, all isomers, both geometric and optical, of a given compound are included within the scope of this invention.

EXAMPLE 1

8-methoxy-5,6-dihydro-2-oxo-2H-naphtho[1,2-b]-pyran-3-carboxylic acid ethyl ester (α-pyrone)

To a mixture of sodium ethoxide prepared from 10.8 parts of sodium hydride and 31 parts of anhydrous ethanol in 300 ml. of anhydrous glyme is added dropwise 67.6 parts of ethyl ethoxymethylenecyanoacete, followed by 70.4 parts of 6-methoxy-1-tetralone dissolved in glyme. The mixture is stirred at 50° C. for 3 hours and is allowed to cool. It is slowly poured into 500 ml. of 3 N hydrochloric acid. The precipitate is collected by filtration and is suspended on 1 liter of water. The mixture is warmed on steam bath for 3 hours and allowed to cool. The solid product is collected by filtration and washed with water. It is recrystallized from ethanol-water mixture to give pure 8-methoxy-5,6-dihydro-2-oxo-2H - naphtho[1,2-b]-pyran-3-carboxylic acid ethyl ester (α-pyrone); M.P. 141–142.5° C.

EXAMPLE 2

The process of Example 1 is repeated but substituting an equivalent amount of indicated "1-tetralone" for 6-methoxy-1-tetralone used in Example 1 to obtain the indicated "α-pyrone."

Ex.	1-tetralone	α-Pyrone
2	6-ethoxy-1-tetralone	8-ethoxy-5,6-dihydro-2-oxo-2H-naphtho [1,2-b]-pyran-3-carboxylic acid ethyl ester; M.P. 147.5–148.5° C.

EXAMPLE 3

The process of Example 1 is repeated using 6-acetoxy-1-tetralone instead of the 6-methoxy-1-tetralone of Example 1 to produce 8-hydroxy-5,6-dihydro-2-oxo-2H-naphtho-[1,2-b]-pyran-3-carboxylic acid ethyl ester.

The above α-pyrone is dissolved in 300 ml. of acetyl chloride and is heated under reflux for 3 hours. The excess acetyl chloride is removed by evaporation under reduced pressure to give 8-acetoxy-5,6-dihydro-2-oxo-2H-naphtho-[1,2-b]-pyran-3-carboxylic acid ethyl ester.

EXAMPLE 4

A solution of 0.2 mole of 8-methoxy-5,6-dihydro-2-oxo-2H-naphtho[1,2-b]pyran-3-carboxylic acid ethyl ester in 200 ml. of benzene is heated at 200° C. with 3,000 atmospheres of ethylene for 20 hours in a suitable pressure vessel. The mixture is cooled. The benzene is evaporated and the solid residue is isolated. It is recrystallized from 95% ethanol to give pure 7-methoxy-2,3,4,4',9,10-hexahydro - 2,4' - ethanophenanthrene-2-carboxylic acid ethyl ester; M.P. 92–92.5° C.

Analysis.—Calcd. for $C_{20}H_{24}O_3$ (percent): C, 76.89; H, 7.74. Found (percent): C, 77.17; H, 7.81.

EXAMPLES 5 and 6

The procedure of Example 4 is repeated substituting an equivalent amount of the listed "α-pyrone" for the 8-methoxy - 5,6-dihydro - 2 - oxo-2H-naphtho[1,2-b]pyran-3-carboxylic acid ethyl ester of Example 4 to obtain the indicated ethanophenanthrene product.

Ex.	α-Pyrone	Ethanophenanthrene
5	8-ethoxy-5,6-dihydro-2-oxo-2H-naphtho[1,2-b]pyran-3-carboxylic acid ethyl ester.	7-ethoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
6	8-acetoxy-5,6-dihydro-2-oxo-2H-naphtho[1,2-b)pyran-3-carboxylic acid ethyl ester.	7-acetoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.

EXAMPLE 7

A solution of 0.2 mole of 5,6-dihydro-2-oxo-2H-naphtho[1,2-b]pyran-3-carboxylic acid ethyl ester in 200 ml.

of benzene is heated at 200° C. with 1,000 atmospheres of 2-cis-butene for 18 hours in a suitable pressure vessel. The mixture is cooled. The benzene is evaporated and the solid residue is isolated. The crude 3,4-cis-dimethyl-3,4,9,10-tetrahydrophenanthrene - 2 - carboxylic acid ethyl ester is redissolved in 200 ml. of benzene and the resulting solution is heated at 200° C. with 3,000 atmospheres of ethylene for 20 hours in a suitable pressure vessel. The mixture is cooled. The benzene is evaporated and the crude product is chromatographed on silicic acid with chloroform as the eluent. Two main fractions are obtained and their i.r. and n.m.r. spectra show them to be exo-3,4 - cis - dimethyl-2,3,4,4',9,10 - hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester and endo-3,4-cis-dimethyl - 2,3,4,4',9,10 - hexahydro - 2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.

EXAMPLE 8–11

The procedure of Example 7 is repeated substituting an equivalent amount of the indicated "α-pyrone" for the 5,6 - dihydro - 2 - oxo-2H-naphtho[1,2-b]pyran-3-carboxylic acid ethyl ester and substituting the indicated 1,2-dialkyl "ethylene" for 2-cis-butene of Example 7 to obtain the indicated ethanophenanthrene. The geometrical isomers are separated by means of chromatograph on silicic acid, fractional crystallization of distillation.

Ex.	α-Pyrone	Ethylene	Ethanophenanthrene
8	8-methoxy-5,6-dihydro-2-oxo-2H-naphtho-[1,2-b]pyran-3-carboxylic acid ethyl ester.	2-cis-butene	3,4-cis-dimethyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
9	8-methoxy-5,6-dihydro-2-oxo-2H-naphtho [1,2-b]pyran-3-carboxylic acid ethyl ester.	1-butene	3-ethyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester and 4-ethyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
10	8-methoxy-5,6-dihydro-2-oxo-2H-naphtho-[1,2-b]pyran-3-carboxylic acid ethyl ester.	2-cis-pentene.	3-methyl-4-cis-ethyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethano-phenanthrene-2-carboxylic acid ethyl ester and 3-ethyl-4-cis-methyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
11	5,6-dihydro-2-oxo-2H-naphtho[1,2-b]pyran-3-carboxylic acid ethyl ester.	Trans-3-hexene.	3,4-trans-diethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
12	5,6-dihydro-2-oxo-2H-naphtho[1,2-b]pyran-3-carboxylic acid ethyl ester.	2-methyl-3-cis-heptene.	3-iso-propyl-4-cis-n-propyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester and 4-iso-propyl-3-cis-n-propyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.

EXAMPLE 13

To a solution of 15.6 parts of 7-methoxy-2,3,4,4',9,10-hexahydro - 2,4' - ethanophenanthrene - 2 - carboxylic acid ethyl ester dissolved in 200 ml. of THF is added 55 ml. of 1 M borane in THF under nitrogen atmosphere over a period of 15 minutes at 25–30°. After two hours, excess borane is destroyed with 15 ml. of water. The chromic acid solution, prepared from 11 parts of sodium dichromate dihydrate and 8.25 ml. of 96% sulfuric acid and diluted with water to 45 ml., is added to the stirred solution over a period of 15 minutes, maintaining the temperature at 25–30°. After stirring at 30–35° for two hours, the mixture is poured into 500 ml. of water. The aqueous mixture is extracted with chloroform. The chloroform extract is dried over anhydrous magnesium sulfate, filtered, and concentrated. The solid residue is recrystallized from ethanol-water mixture to give pure 7-methoxy - 1,2,3,4,4',9,10,10' - octahydro - 1 - oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.

EXAMPLES 14–18

The procedure of Example 13 is repeated substituting an equivalent amount of the indicated "hexahydro-phenanthrene" for the 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester of Example 13 to obtain the indicated octahydro-1-oxo-phenanthrene product.

Ex.	Hexahydro-phena threne	Octahydro-1-oxophenanthrene
14	7-ethoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	7-ethoxy-1,2,3,4,4'9,10,10'-octahydro-1-oxo-2,4',-ethanophenanthrene-2-carboxylic acid ethyl ester.
15	Exo-3,4-cis-dimethylj2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Exo-3,4-cis-dimethyl-1,2,3,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
16	4-iso-propyl-3-cis-n-propyl-7-acetoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	4-iso-propyl-3-cis-n-propyl-7-acetoxy-1,2,3,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
17	Exo-3-ethyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Eox-3-ethyl-7-methoxy-1,2,3,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
18	Endo-4,methyl-7,methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Endo-4-methyl-7-methoxy-1,2,3,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.

EXAMPLE 19

To a solution of 16.4 parts of 7-methoxy-1,2,3,4,4',9,10,10' - octahydro - 1 - oxo - 2,4' - ethanophenanthrene-2-carboxylic acid ethyl ester dissolved in 100 ml. of THF is added 50 ml. of 1 M methyl magnesium bromide in ethyl ether under nitrogen atmosphere over a period of 15 minutes, maintaining the temperature at —10–0°. After stirring at —10–0° for 3 hours, the mixture is poured into 300 ml. of saturated aqueous ammonium chloride solution. The upper layer is separated, and the aqueous layer extracted with ethyl ether. The combined organic extracts are dried over anhydrous magnesium sulfate, filtered, and concentrated to give 7-methoxy-1-methyl-1-hydroxy - 1,2,3,4,4',9,10,10' - octahydro - 2,4' - ethanophenanthrene-2-carboxylic acid ethyl ester.

To a solution of the crude hydroxy-ester dissolved in 100 ml. of pyridine is added portionwise 9.5 parts of p-toluenesulfonyl chloride with stirring, maintaining the temperature at 25–30°. After stirring at 25–30° for one hour, the mixture is poured into 300 ml. of water. The aqueous mixture is extracted with chloroform several times. The combined chloroform extracts are washed with dilute hydrochloric acid, followed by water, dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue is recrystallized from ethanol-water mixture to give pure 7-methoxy-1-methyl - 2,3,4,4',9,10-hexahydro - 2,4' - ethanophenanthrene - 2 - carboxylic acid ethyl ester.

EXAMPLES 20–25

The procedure of Example 19 is repeated substituting an equivalent amount of the indicated "1-oxophenanthrene" for the 7-methoxy - 1,2,3,4,4',9,10,10' - octahydro-1-oxo-2,4'-ethanophenanthrene - 2 - carboxylic acid ethyl ester, and substituting an equivalent amount of the indicated alkyl "Grignard reagent" for the methyl magnesium bromide of Example 19 to obtain the indicated 1-alkyl-ethanophenanthrene. However, when the ethanophenanthrene-2-carboxylic acid is used instead of its ethyl ester, two equivalent amounts of Grignard reagent is used instead of one equivalent.

Ex.	1-oxophenanthrene	Grignard reagent	1-alkylethanophenanthrene
20	1,2,3,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid.	Ethyl magnesium bromide.	1-ethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid.
21	7-acetoxy-1,2,3,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	n-propyl magnesium bromide.	7-acetoxy-1-n-propyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
22	Exo-3,4-cis-dimethyl-1,2,3,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Iso-propyl magnesium bromide.	Exo-3,4-cis-dimethyl-1-iso-propyl-2-3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
23	Endo-3,4-cis-diethyl-7-methoxy-1,2,3,4,4'-9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid.	n-Butyl magnesium bromide.	Endo-3,4-cis-diethyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid.
24	Exo-3-ethyl-7-methoxy-1,3,2,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Methyl magnesium bromide.	Exo-3-ethyl-1-methyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
25	Endo-3-methyl-7-methoxy-1,2,3,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Methyl magnesium iodide.	Endo-4-methyl-1-methyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.

EXAMPLE 26

A mixture of 0.2 mole of 7 - methoxy - 2,3,4,4',9,10-hexahydro - 2,4' - ethanophenanthrene - 2 - carboxylic acid ethyl ester, 200 ml. of ethyl acetate, and 3 parts of 10% palladium on charcoal is hydrogenated at an initial pressure of 50 p.s.i. in a shaker apparatus. When uptake of hydrogen is complete, the catalyst is filtered off, and the filtrate is evaporated at reduced pressure to give 7-methoxy - 1,2,3,4,4',9,10,10' - octahydro - 2,4' - ethanophenanthrene - 2 - carboxylic acid ethyl ester; M.P. 65.5–67.5°.

Analysis.— Calcd. for $C_{20}H_{26}O_3$ (percent): C, 76.40; H, 8.34. Found (percent): C, 76.69; H, 8.40.

EXAMPLES 27–33

The procedure of Example 26 is repeated substituting an equivalent amount of the indicated "hexahydrophenanthrene" for the 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene - 2 - carboxylic acid ethyl ester of Example 26 to obtain the listed octahydro derivative. When this procedure results in the formation of geometric isomers, they can be separated by means of chromatograph on silicic acid or fractional crystallization.

Ex.	Hexahydro-phenanthrene	Octahydro-phenanthrene
27	7-ethoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	7-ethoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester; M.P. 70–72°.
28	7-methoxy-1-methyl-2,3,4,4',-9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	7-methoxy-1-methyl-1,2,3,4,4',9,-10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
29	Exo-3,4-cis-diethyl-1-n-propyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Exo-3,4-cis-diethyl-1-n-propyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
30	3-methyl-4-trans-ethyl-7-acetoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	3-methyl-4-trans-ethyl-7-acetoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
31	Exo-3-ethyl-1-methyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Exo-3-ethyl-1-methyl-7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
32	Endo-4-methyl-1-methyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Endo-4-methyl-1-methyl-7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
33	Exo-3-methyl-7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Exo-3-methyl-7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.

EXAMPLE 34

Sodium hydride (0.1 mole as a 55% dispersion in mineral oil) is washed with several portions of n-pentane to remove the mineral oil. Dimethyl sulfoxide (50 ml.) is added, and the mixture is heated at 75–80° for 45 minutes, or until the evolution of hydrogen ceases. The resulting solution of methylsulfinyl carbanion is cooled in an ice-water bath, and 0.1 mole of methyltriphenylphosphonium bromide in 100 ml. of warm dimethyl sulfoxide is added. The resulting dark red solution of the ylide is stirred at room temperature for 10 minutes.

To the above red solution is added a solution of 0.11 mole of 7-methoxy-1,2,3,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester in 50 ml. of dimethyl sulfoxide, and the reaction mixture is stirred at room temperature for 30 minutes. After cooling in an ice-bath, the mixture is filtered. The filtrate is diluted with 500 ml. of water. The aqueous mixture is extracted with ethyl ether. The ether solution is dried over anhydrous magnesium sulfate, filtered, and concentrated. The residue is crystallized from 95% ethanol to give 7-methoxy-1-methylene-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.

A mixture of the above unsaturated ester, 100 ml. of ethyl acetate, and 1.5 parts of 10% palladium on charcoal is hydrogenated at an initial pressure of 50 p.s.i. in a shaker apparatus. When uptake of hydrogen is complete, the catalyst is filtered off, and the filtrate is evaporated at reduced pressure to give 7-methoxy-1-methyl-1,2,3,4,4',9,10,10'-octahydro - 2,4' - ethanophenanthrene-2-carboxylic acid ethyl ester.

EXAMPLES 35–36

The procedure of Example 34 is repeated substituting an equivalent amount of the indicated "1-oxo-phenanthrene" for the 7-methoxy-1,2,3,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene - 2 - carboxylic acid ethyl ester and substituting an equivalent amount of the indicated "Wittig reagent" for the methyltriphenylphosphonium bromide of Example 34 to obtain the listed 1-alkyl-octahydro product.

Ex.	1-oxo-phenanthrene	Wittig reagent	1-alkyl octahydropenenanthrene
35	7-acetoxy-1,2,3,4, 4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Ethyltriphenyl phosphonium bromide.	7-acetoxy-1-ethyl-1,2,3,4,4',9,10,10', octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.
36	Exo-3,4-cis-dimethyl-1,2,3,4,4',9,10,10'-octahydro-1-oxo-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	n-Butyltriphenylphosphonium bromide.	Exo-3,4-cis-dimethyl-1-n-butyl-1,2,3,4,4'-9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.

EXAMPLE 37

A mixture of 1.6 mole of 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene - 2 - carboxylic acid ethyl ester, 2.0 mole of powdered sodium hydroxide, and 1000 ml. of diethylene glycol is heated at 160° C. for 2 hours under nitrogen atmosphere. The mixture is cooled and is poured into 4000 ml. of water. The solution is acidified with 400 ml. of 6 N hydrochloric acid. The precipitate is filtered off, is washed with water, and is recrystallized from acetonitrile to give 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene - 2 - carboxylic acid; M.P. 213–216°.

Analysis.—Calcd. for $C_{18}H_{20}O_3$ (percent): C, 76.03; H, 7.09. Found (percent): C, 76.24; H, 7.07.

EXAMPLES 38–46

The procedure of Example 37 is repeated substituting an equivalent amount of the indicated "ester" for the 7-methoxy - 2,3,4,4',9,10 - hexahydro - 2,4' - ethanophenanthrene-2-carboxylic acid ethyl ester of Example 37 to obtain the listed carboxylic acid.

Ex.	Ester	Carboxylic acid
38	7-methoxy-1,2,3,4,4', 9,10,10'-octahydro-2,4'-ethano-phenanthrene-2-carboxylic acid ethyl ester.	7-methoxy-1,2,3,4,4',9,10-10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid; M.P. 258–261°.
39	7-ethoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethano-phenanthrene-2-carboxylic acid ethyl ester.	7-ethoxy-1,2,3,4,4'.9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid.
40	7-ethoxy-2,3,4,4',9,10-hexa-hydro-2,4'-ethano-phenanthrene-2-carboxylic acid ethyl ester.	7-ethoxy-2,3,4,4',9,10-hexa-hydro-2,4'-ethanophenan-threne-2-carboxylic acid.
41	1-methyl-7-methoxy-1,2,3,4,4', 9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	1-methyl-7-methoxy-1,2,3,4,4', 9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid.
42	1-n-propyl-7-ethoxy-2,3,4,4',9, 10-octahydro-2,4'-ethano-phenanthrene-2-carboxylic acid ethyl ester.	1-n-propyl-7-ethoxy-2,3,4,4',9, 10-octahydro-2,4'-ethano-phenanthrene-2-carboxylic acid.
43	Exo-3,4-cis-diethyl-1,2,3,4,4',9, 10,10'-hexahydro-2,4'-ethano-phenanthrene-2-carboxylic acid ethyl ester.	Exo-3,4-cis-diethyl-1,2,3,4,4',9, 10,10'-hexahydro-2,4'-ethano-phenanthrene-2-carboxylic acid.
44	Endo-3,4-cis-di-iso-propyl-7-methoxy-1-methyl-2,3,4,4',9, 10-hexahydro-2,4'-ethano-phenanthrene-2-carboxylic acid ethyl ester.	Endo-3,4-cis-di-iso-propyl-7-methoxy-1-methyl-2,3,4,4',9, 10-hexahydro-2,4'-ethano-phenanthrene-2-carboxylic acid.
45	Endo-3-ethyl-7-methoxy-1,2,3, 4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-car-boxylic acid ethyl ester.	Endo-3-ethyl-7-methoxy-1,2,3, 4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-car-boxylic acid.
46	Endo-4-ethyl-1-methyl-2,3,4, 4',9,10-hexahydro-2,4'-ethanophenanthrene-2-car-boxylic acid ethyl ester.	Endo-4-ethyl-1-methyl-2,3,4, 4',9,10-hexahydro-2,4'-ethanophenanthrene-2-car-boxylic acid.

EXAMPLE 47

A mixture of 0.15 mole of 7-acetoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene - 2 - carboxylic acid ethyl ester, 0.5 mole of powdered sodium hydroxide, and 500 ml. of diethylene glycol is heated at 160° C. for 2 hours under nitrogen atmosphere. The mixture is cooled and is poured into 2000 ml. of water. The mixture is acidified with 100 ml. of 6 N hydrochloric acid. The precipitate is filtered off, is washed with water, and dried to give 7-hydroxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid.

Repeating the procedure of Example 47 with an equivalent amount of 7-acetoxy-1-n-propyl-1,2,3,4,4',-9,10,10'-octahydro-2,4'-ethanophenanthrene - 2 - carboxylic acid ethyl ester yields 7-hydroxy-1-n-propyl-1,2,3,4,4', 9,10,10'-octahydro-2,4'-ethanophenanthrene - 2 - carboxylic acid.

EXAMPLE 48

A mixture of 0.1 mole of 7-acetoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene - 2 - carboxylic acid ethyl ester, 0.11 mole of pyrrolidine, and 300 ml. of benzene is heated under reflux for 3 hours. The mixture is cooled and washed with water, dried over anhydrous magnesium sulfate, filtered, and concentrated at reduced pressure to give 7-hydroxy-2,3,4,4',9,10-hexahydro - 2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.

Repeating the procedure of Example 48 with an equivalent amount of 7-acetoxy-endo-3,4-cis-diethyl-1,2,3,4,4',9,10,10'-octahydro - 2,4' - ethanophenanthrene - 2-carboxylic acid ethyl ester yields 7-hydroxy-endo-3,4-cis-diethyl-1,2,3,4,4',9,10,10'-octahydro - 2,4' - ethanophenanthrene-2-carboxylic acid ethyl ester.

EXAMPLE 49

A Sohxlet extractor with Linde molecular sieve type 5A, 1/16 inch in the thimble and 0.1 mole of 7-methoxy-1,2,3,4,4',9,10,10'-octahydro - 2,4' - ethanophenanthrene-2-carboxylic acid, 0.5 g. of p-toluenesulfonic acid, and 250 ml. of methyl alcohol in the flask is refluxed for 16 hours. The solution is cooled and is evaporated. The residue is dissolved in chloroform. The solution is washed with 5% $NaHCO_3$ solution, dried over anhydrous magnesium sulfate, filtered, and evaporated to give 7-methoxy-1,2,3,4,4',9,10,10'-octahydro - 2,4' - ethanophenanthrene-2-carboxylic acid methyl ester.

EXAMPLES 50–51

The procedure of Example 49 is repeated, substituting an equivalent amount of the indicated "acid" for the 7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4' - ethanophenanthrene-2-carboxylic acid of Example 49 and using the appropriate alcohol for the methanol of Example 49 to obtain the listed "ester."

Ex.	Acid	Ester
50	7-hydroxy-1-methyl-2, 3, 4, 4', 9, 10-hexahydro-2, 4', ethanophenanthrene-2-carboxylic acid.	7-hydroxy-1-methyl-2, 3, 4, 4', 9, 10-hexahydro-2, 4'-ethanophenanthrene-2-carboxylic acid n-propyl ester.
51	Exo-3, 4-cis-n-propyl-1, 2, 3, 4, 4', 9, 10, 10'-octahydro-2, 4'-ethanophenanthrene-2-carboxylic acid.	Exo-3, 4-cis-n-propyl-1, 2, 3, 4, 4', 9, 10, 10'-octahydro-2, 4'-ethanophenanthrene-2-carboxylic acid methyl ester.

EXAMPLE 52

As will be recognized by those skilled in the art, salts of the ethanophenanthrene-2-carboxylic acids can be readily formed in the following manner. A mixture of 0.1 mole of carboxylic acid and 0.1 equivalent of alkali hydroxide, alkaline earth carbonate, or ammonium hydroxide in 250 ml. of water is heated until all of the acid has dissolved. An excess of ammonium hydroxide is advantageous due to the tendency to lose ammonia during the heating. The solution is allowed to cool, and the salt is allowed to crystallize. The crystals are collected by filtration, washed with a minimum of cold water, and dried to give salts such as the following:

7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid sodium salt

7-ethoxy-1-ethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid potassium salt

7-hydroxy-endo-3,4-cis-dimethyl-2,3,4,4',9,10 - hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ammonium salt

7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid magnesium salt

EXAMPLE 53

A mixture of 0.03 mole of 7-methoxy-1,2,3,4,4',9,10,10'-octahydro - 2,4' - ethanophenanthrene-2-carboxylic acid ethyl ester, 0.1 mole of lithium aluminum hydride, and 150 ml. of THF is refluxed under a nitrogen atmosphere for 4 hours. The mixture is cooled and water is cautiously added until the gray lithium aluminum hydride is converted to a white product. The precipitate is filtered off and is washed with THF. The filtrate is dried over anhydrous magnesium sulfate, filtered, and concentrated. The solid residue is recrystallized from methylcyclohexane to give pure 7-methoxy-1,2,3,4,4',9,10,10' - octahydro - 2,4'-ethanophenanthrene-2-methanol; M.P. 113.5–115°.

Analysis.—Calcd. for $C_{18}H_{24}O_2$ (percent): C, 79.37; H, 8.88. Found (percent): C, 79.52; H, 8.82.

EXAMPLES 54–56

The procedure of Example 53 is repeated, substituting an equivalent amount of the indicated starting material for the 7-methoxy-1,2,3,4,4',9,10,10' - octahydro - 2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester of Example 53 to obtain the listed "methanol."

Ex.	Starting material	Methanol
54	7-methoxy-2, 3, 4, 4', 9, 10-hexahydro-2, 4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	7-methoxy-2, 3, 4, 4', 9, 10-hexahydro-2, 4'-ethanophenanthrene-2-methanol, M.P. 106.5–108.5° C.
55	7-hydroxy-1-n-propyl-2, 3, 4, 4', 9, 10-hexahydro-2, 4'-ethanophenanthrene-2-carboxylic acid.	7-hydroxy-1-n-propyl-2, 3, 4, 4', 9, 10-hexahydro-2, 4'-ethanophenanthrene-2-methanol.
56	7-ethoxy-exo-3, 4-cis-diethyl-2, 3, 4, 4', 9, 10-hexahydro-2, 4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	7-ethoxy-eso-3, 4-cis-diethyl-2, 3, 4, 4', 9, 10-hexahydro-2, 4'-ethanophenanthrene-2-methanol.

EXAMPLE 57

To a solution of 0.01 mole of 7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene - 2 - methanol in 50 ml. of dry pyridine is added 5 ml. of acetic anhydride. The solution is allowed to stand for 16 hours. Then 5 ml. of water is added, and the solution is allowed to stand for 4 hours. The solution is poured into a mixture of 200 parts of ice and 200 ml. of 6 N HCl. When the ice is melted, the precipitate is filtered off, is washed thoroughly with water, and is dried to give 7-methoxy - 1,2,3,4,4',9,10,10' - octahydro - 2,4' - ethanophenanthrene-2-methanol acetate ester.

EXAMPLES 58–63

The procedure of Example 57 is repeated using the indicated starting "alcohol" and acid chloride or acid anhydride to give the indicated product.

Ex.	Alcohol	Acid chloride or anhydride	Product
58	7-methoxy-1-ethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol.	Acetic anhydride.	7-methoxy-1-ethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol acetic acid ester.
59	7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol.	Propionyl chloride.	7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol propionic acid ester.
60	Exo-3,4-cis-di-n-butyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol.	Succinic anhydride.	Exo-3,4-cic-di-n-butyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol succinic acid mono-ester.
61	1-iso-propyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol.	Adipyl chloride.	1-iso-propyl-1,2,3,4,4',9,10,10'-octahydro-2,4',ethanophenanthrene-2-methanol adipic acid mono-ester.
62	7-hydroxy-1-ethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol.	iso-butyrl chloride.	7-iso-butyroxy-1-ethyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-methanol iso-butyric acid ester.
63	7-hydroxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol.	Acetic anhydride.	7-acetoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-methanol acetic acid ester.

Acylation at the phenolic hydroxyl can be accomplished in the following manner.

EXAMPLE 64

A solution of 0.1 mole of 7-hydroxy-1,2,3,4,4',9,10,10' - octahydro - 2,4' - ethanophenanthrene - 2-methanol in 50 ml. of pyridine is treated with 0.1 mole of acetic anhydride according to the procedure of Example 57, to give 7-acetoxy - 1,2,3,4,4',9,10,10' - octahydro - 2,4'-ethanophenanthrene-2-methanol.

EXAMPLE 65

A solution of 0.1 mole of 7-acetoxy-1,2,3,4,4',9,10,10' - octahydro - 2,4' - ethanophenanthrene-2-methanol acetic acid ester and 0.1 mole of potassium carbonate in 100 ml. of 90% ethanol is refluxed for 16 hours. The resulting solution is cooled, poured into ice-water, and acidified with hydrochloric acid. The precipitate is filtered off, is washed with water, and is dried to give 7-hydroxy-1,2,3,4,4',9,10,10'-octahydro - 2,4' - ethanophenanthrene - 2-methanol acetic acid ester.

EXAMPLE 66

A mixture of 0.05 mole of 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid and 50 ml. of thionyl chloride is heated under reflux for 30 minutes and cooled. The excess thionyl chloride is removed by concentration at reduced pressure to give 7-methoxy - 2,3,4,4',9,10 - hexahydro - 2,4' - ethanophenanthrene-2-carboxylic acid chloride.

The above acid chloride is dissolved in 50 ml. of diethylene glycol dimethyl ether (diglyme) and cooled to —70°. To the cooled solution is added 0.05 mole of lithium tri-t-butoxy aluminum hydride. The mixture is stirred at —70° for 3 hours and slowly poured into 250 ml. of ice-water. The precipitate is collected by filtration, washed thoroughly with water, and dried to give 7-methoxy-2,3,4,4',9,10 - hexahydro - 2,4' - ethanophenanthrene-2-carboxyaldehyde.

EXAMPLES 67–68

The procedure of Example 66 is repeated using indicated starting "carboxylic acid" to give the indicated "carboxaldehyde."

Ex.	Carboxylic acid	Carboxaldehyde
67	1,2,3,4,4',9,10,10'-octahydro-1-methyl-2,4'-ethanophenanthrene-2-carboxylic acid.	1,2,3,4,4',9,10,10'-octahydro-1-methyl-2,4'-ethanophenanthrene-2-carboxaldehyde.
68	7-acetoxy-1-ethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid.	7-acetoxy-1-ethyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxaldehyde.

EXAMPLE 69

A solution of 0.1 mole of 7-acetoxy-1-ethyl-2,3,4,4',9,10-octahydro - 2,4' - ethanophenanthrene-2-carboxaldehyde and 0.1 mole of potassium carbonate in 100 ml. of 90% ethanol is treated according to the procedure of Example 65, to give 7-hydroxy-1-ethyl-2,3,4,4',9,10-octahydro-2,4'-ethanophenanthrene-2-carboxaldehyde.

EXAMPLE 70

A mixture of 0.05 mole of 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid and 50 ml. of thionyl chloride is heated under reflux for 30 minutes and cooled. This solution is poured into a cold, stirred, aqueous ammonium hydroxide. The precipitate forms and this precipitate is collected by filtration, washed with water, and dried to give 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxamide.

EXAMPLES 71–73

The procedure of Example 70 is repeated substituting equivalent amount of the indicated "acid" for the 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid and an aqueous solution of the indicated

"amine" for the ammonium hydroxide solution of Example 70 to obtain the indicated product.

Ex.	Acid	Amine	Product
71	7-methoxy-1, 2, 3, 4, 4', 9, 10, 10'-octahydro-2, 4'-ethanophenanthrene-2-carboxylic acid.	Methylamine	7-methoxy-N-methyl-1, 2, 3, 4, 4', 9, 10, 10' octahydro-2, 4'-ethanophenanthrene-2-carboxamide.
72	7-methoxy-1-n-propyl-2, 3, 4, 4', 9, 10-hexahydro-2, 4'-ethanophenanthrene-2-carboxylic acid.	Diethylamine	N, N-diethyl-7-methoxy-1-n-propyl-2, 3, 4, 4', 9, 10-hexahydro-2, 4'-ethanophenanthrene-2-carboxamide.
73	Exo-3, 4-cis-dimethyl-2, 3, 4, 4', 9, 10-hexahydro-2, 4'-ethanophenanthrene-2-carboxylic acid.	Pyrrolidine	N, N-tetramethylene-exo-3, 4-cis-dimethyl-2, 3, 4, 4', 9, 10-hexahydro-2, 4'-ethanophenanthrene-2-carboxamide.

EXAMPLE 74

A mixture of ten parts of 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester and fifty parts anhydrous ammonia is charged to an autoclave and is heated with shaking at 160° C. for 16 hours at autogenous pressure. The mixture is cooled and excess ammonia is evaporated to give 7-methoxy-2,3,4,4',9,10-hexahydro - 2,4' - ethanophenanthrene-2-carboxamide.

EXAMPLES 75–76

The procedure of Example 77 is repeated, substituting an equivalent amount of the indicated "ester" and indicated "amine" respectively for the 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene - 2 - carboxylic acid ethyl ester, and ammonia of Example 74 to obtain the indicated product.

Ex.	Acid	Amine	Product
75	7-hydroxy-1-methyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester.	Methylamine	N-methyl-7-hydroxy-1-methyl-2,3,4,4',-9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxamide.
76	7-hydroxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid methyl ester.	Ammonia	7-hydroxy-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxamide.

EXAMPLE 77

A solution of 0.01 mole of 7-hydroxy-1,2,3,4,4',9,10,10'-octahydro-2,4' - ethanophenanthrene - 2-carboxamide in 50 ml. of dry pyridine is treated with 0.01 mole of acetic anhydride according to the procedure of Example 57 to give 7 - acetoxy - 1,2,3,4,4',9,10,10'-octahydro - 2,4'-ethanophenanthrene-2-carboxamide.

EXAMPLE 78

A mixture of 0.01 mole of 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene - 2 - carboxylic acid in 30 ml. of benzene is treated with 5 ml. of thionyl chloride and is stirred for 1 hour. The solution is evaporated at reduced pressure. The residue is dissolved in 20 ml. of pyridine. A solution of 0.05 mole of hydroxylamine hydrochloride in 20 ml. of pyridine is added, and the mixture is stirred for 16 hours. The mixture is poured into a mixture of 500 ml. of IN hydrochloric acid and 200 parts of ice. The precipitate is filtered off, is washed with water, and is dried to give 7-methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene - 2 - carboxyhydroxamic acid.

EXAMPLE 79

A solution of 0.02 mole of 7-methoxy-1,2,3,4,4',9,10,10'-octahydro-2,4' - ethanophenanthrene - 2 - carboxylic acid ethyl ester and 0.1 mole of 99% hydrazine in 50 ml. of amyl alcohol is heated under reflux for 3 days. The product is evaporated at reduced pressure to give 7-methoxy-1,2,3,4,4',9,10,10' - octahydro - 2,4' - ethanophenanthrene-2-carboxylic acid hydrazide.

EXAMPLE 80

A solution of 0.01 mole of 7-methoxy-1-methyl-2,3,4,4',9,10 - hexahydro - 2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester and 0.01 mole of methylhydrazine in 100 ml. of amyl alcohol is heated at 150° C. in an autoclave at autogenous pressure for 16 hours. The mixture is cooled and evaporated to give N'-methyl-7-methoxy-1-methyl - 2,3,4,4',9,10 - hexahydro - 2,4' - ethanophenanthrene-2-carboxylic acid hydrazide.

When the procedure of Example 80 is repeated, substituting an equivalent amount of 7-hydroxy-2,3,4,4',9,10 - hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester and 1,1-di-methylhydrazine for the 7-methoxy - 1 - methyl-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester and methylhydrazine, respectively, of Example 80, N',N'-dimethyl-7-hydroxy - 2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid hydrazide.

EXAMPLE 81

A mixture of 3.14 parts of N',N'-dimethyl-7-hydroxy-2,3,4,4',9,10 - hexahydro - 2,4' - ethanophenanthrene-2-carboxylic acid hydrazide, 54 parts of acetic anhydride, and 4 parts of anhydrous sodium acetate is heated under reflux for one hour. The mixture is allowed to cool and 20 parts of water is added dropwise. The mixture is allowed to stand for 12 hours and is evaporated at reduced pressure. The residue is treated with a mixture of 5% sodium bicarbonate solution and chloroform. The chloroform extract is washed with water, is dried with anhydrous magnesium sulfate, filtered, and concentrated to give N',N'-dimethyl-7-acetoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid hydrazide.

The compounds of Formula I can be administered to prevent pregnancy in warm-blooded animals according to the method of this invention by any suitable means. For example, administration can be parenterally, that is subcutaneously or intramuscularly. Alternatively administration can be by the oral or rectal route. These compounds can be administered in single or divided doses for from 0 to 15 days after coitus.

In general, the dosage for administering the compounds of this invention to warm-blooded animals is in the range of approximately 0.001–50 mg./kg.-day. It is preferred that the compounds of this invention be administered at a dosage of from 0.005–10 mg./kg.-day with a dosage of from 0.01–5 mg./kg.-day being most preferred.

It is also preferred that these compounds be administered in a single oral dose after coitus, but before estimated time of implantation of the fertilized egg in the uterus.

The compounds of this invention are orally effective when administered to warm-blooded animals as is demonstrated by the following test. This test particularly demonstrates that the compounds of this invention demonstrate outstanding inhibition of pregnancy in rats.

EXAMPLE 82

Immature female rats (28 days old) are induced into precocious puberty with a single dose of pregnant mare's serum gonadotrophin and then are mated with normal males. 7 - methoxy-2,3,4,4',9,10-hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid suspended in sesame oil is orally administered in graded doses to numerically equal groups of these female rats for six days starting on the day of finding sperm or a vaginal plug. One week after mating, the animals are killed and their uteri are examined for implantation sites. If any are found, the animal is considered pregnant. Control animals have a mean of eight implantation sites. The dose level at which fifty percent of the animals show no evidence of pregnancy, the ED_{50}, is between 0.08 and 0.31 mg./kg.-day.

The test of Example 82 is repeated substituting 7-methoxy - 2,3,4,4',9,10 - hexahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester for the compound of Example 82. The ED_{50}, determined as described above, is found to be between 0.08–0.31 mg./kg.-day.

The test of Example 82 is repeated substituting 7-methoxy - 1,2,3,4,4',9,10 - octahydro-2,4'-ethanophenanthrene-2-methanol for the compound of Example 82. The ED_{50}, determined as described above, is found to be between 0.31–1.25 mg./kg.-day.

The compounds for the method of this invention can also be employed with equally satisfactory results to prevent pregnancy in other laboratory animals such as mice, guinea pigs, rabbits, monkeys and chimpanzees and are also effective in preventing pregnancy in domestic animals such as swine, cows, sheep and horses. In small animals it is usually convenient to administer the compounds of this invention in the form of a capsule, or incorporated in the feed of the animal. However, when these compounds are administered to large animals, it is often more convenient to administer them parenternally.

The compounds of Formula I can be employed in useful compositions according to the present invention in such dosage forms as tablets, capsules, powder packets, or liquid solutions, suspensions, or elixirs, for oral administration or liquid solutions for parenteral use, and in certain cases, suspensions for parenteral use. In such compositions, the active ingredient will ordinarily always be present in an amount of at least 0.01% by weight based on the total weight of the composition and not more than 90% by weight.

Besides the active ingredient of this invention, the composition will contain a solid or liquid non-toxic pharmaceutical carrier for the active ingredient.

In one embodiment of a pharmaceutical composition of this invention, the solid carrier is a capsule which can be of the ordinary gelatin type. The capsule will contain from about 0.1–75% by weight of a compound of Formula I and 99.9–25% of a carrier.

In another embodiment, the active ingredient is tableted with or without adjuvants. In yet another embodiment, the active ingredient is put into powder packets and employed. These capsules, tablets, and powders will generally constitute from about 0.5% to about 95% and preferably from 1% to 50% by weight of active ingredient. These dosage forms preferably contain from about 0.5 to about 250 milligrams of active ingredient, with from about 1 milligram to about 50 milligrams most preferred.

The pharmaceutical carrier can, as previously indicated, be a sterile liquid such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, for example peanut oil, soybean oil, mineral oil, sesame oil, and the like. In general water, saline, aqueous dextrose (glucose) and related sugar solutions and glycols such as propylene glycol or polyethylene glycols are preferred liquid carriers, particularly for injectable solutions. Sterile injectable solutions such as saline will ordinarily contain from about 0.05% to 25%, and preferably about 0.1% to 5% by weight of the active ingredient.

As mentioned above, oral administration can be in a suitable suspension, syrup or elixir in which the active ingredient ordinarily will constitute from about 0.01 to 5% and preferably about 0.05 to 1% by weight. The pharmaceutical carrier in such composition can be an aqueous vehicle such as an aromatic water, a syrup or a pharmaceutical mucilage.

Suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E. W. Martin, a well-known reference text in this field.

In addition to the exemplary illustrations above, the following examples further explain one aspect of the present invention.

EXAMPLE 83

A large number of unit capsules are prepared for oral administration by filling standard two-piece hard gelatin capsules with 10 milligrams of powdered 7-methoxy-2,3,4,4',9,10 - hexahydro - 2,4' - ethanophenanthrene - 2 - carboxylic acid, (methoxyphenyl)bicyclo [2.2.2]oct-2-ene-1-carboxylic acid, sodium salt, 342 milligrams of lactose, 8 mg. of magnesium stearate and 40 mg. of talc.

EXAMPLE 84

A large number of unit capsules are prepared for oral administration by filling soft gelatin capsules with a solution of 7-methoxy-1,2,3,4,4',9,10,10' - octahydro-2,4'-ethanophenanthrene-2-methanol in sesame oil.

EXAMPLE 85

A large number of tablets are prepared by conventional procedures so that the dosage unit is 5 milligrams of 7-methoxy-2,3,4,4',9,10-hexahydro - 2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester, 82.9 milligrams of anhydrous lactose, 2 milligrams of magnesium stearate, 10 milligrams of microcrystalline cellulose and 0.1 mg. pyrogenic silica.

EXAMPLE 86

A large number of tablets are prepared by conventional procedures so that the dosage unit is 1 milligram of 7-hydroxy-1-methyl - 2,3,4,4',9,10 - hexahydro - 2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester, 86.9 milligrams of anhydrous lactose, 2 milligrams of magnesium stearate, 10 milligrams of microcrystalline cellulose and 0.1 mg. pyrogenic silica.

EXAMPLE 87

A large number of tablets are prepared by conventional procedures so that the dosage unit is 10 milligrams of 7-acetoxy - 1 - propyl-1,2,3,4,4',9,10,10'-octahydro-2,4'-ethanophenanthrene-2-carboxylic acid ethyl ester, 77.9 milligrams of anhydrous lactose, 2 milligrams of magnesium stearate, 10 milligrams of microcrystalline cellulose and 0.1 mg. pyrogenic silica.

In other tablet formulations from one to seven percent of the tatal weight of the dosage form can be comprised of a lubricant or glidant such as talc, stearic acid, magnesium stearate or the like in place of the pyrogenic silica of the above formulations.

Other binders such as starch, ethylcellulose, polyethyleneglycol 4,000 or the like can be substituted for the anhydrous lactose of the above formulations with satisfactory results.

Other fillers which can be substituted for the microcrystalline cellulose of the above formulation include lactose, manitol or the like.

In some formulations, it is also preferred to include a typical disintegrating agent such as methylcellulose, veegum or starch.

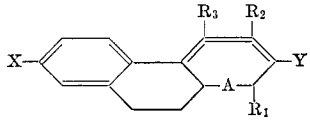
A large variety of compositions according to this invention can thus readily be made by substituting other compounds for this invention, and including specifically,

but not limited to, compounds for this invention that have specifically been named hereinbefore. The compounds will be used in the amounts indicated in accordance with procedures well known and desrcibed in the Martin text mentioned above.

Since many different embodiments of the invention can be made without departing from the spirit and scope thereof, it is to be understood that the invention is not limited by the specific illustration except to the extent defined in the following claims.

What is claimed is:

1. A compound of the formula

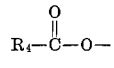


where

A is selected from the group consisting of a single bond and a double bond;

R_1, R_2 and R_3 can be the same or different and are selected from the group consisting of hydrogen and alkyl of one through six carbons;

X is selected from the group consisting of hydrogen, HO, RO and



wherein R is an alkyl of one through four carbons and R_4 is hydrogen or alkyl of one through twelve carbons with the limitation that when X is hydrogen at least one of R_1, R_2 and R_3 must be alkyl of one through six carbons; and

R_5 is hydrogen, alkyl of one through six carbons, and a non-toxic pharmaceutically acceptable salt-forming cation.

2. A compound of claim 1 where

A is a single bond or a double bond;

R_1 is hydrogen;

R_2 is hydrogen;

R_3 is hydrogen;

X is hydroxy, methoxy, ethoxy, or acetoxy; and

Y is COOH.

3. A compound of claim 1 where

A is a single bond or a double bond;

R_1, R_2 and R_3 can be the same or different and are selected from the group consisting of hydrogen, methyl and ethyl with the limitation that at least one of R_1, R_2 and R_3 must be methyl or ethyl;

X is hydroxy, methoxy or acetoxy; and

Y is $COOR_5$ where R_5 is selected from the group consisting of hydrogen, methyl, ethyl, sodium, potassium or ammonium.

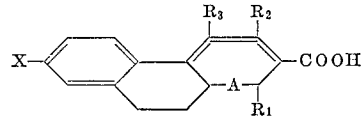
4. A compound of claim 1 which is 7-methoxy-2,3,4,-4',9,10-hexahydro-2,4'-ethanophenanthrene - 2-carboxylic acid.

5. A compound of claim 1 which is 7-methoxy-1,2,3,-4,4',9,10,10' - octahydro - 2,4'-ethanophenanthrene-2-carboxylic acid.

6. A compound of claim 1 which is 7-methoxy-2,3,-4,4',9,10 - hexahydro - 2,4' - ethanophenanthrene-2-carboxylic acid ethyl ester.

7. A compound of claim 1 which is 7-methoxy-1,2,3,-4,4',9,10,10' - octahydro - 2,4' - ethanophenanthrene-2-carboxylic acid ethyl ester.

8. A compound of the formula:

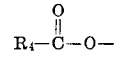


where

A is selected from the group consisting of a single bond and a double bond;

R_1, R_2 and R_3 can be the same or different and are selected from the group consisting of hydrogen and alkyl of one through six carbon atoms; and

X is selected from the group consisting of hydrogen, HO—, RO— and



wherein

R is an alkyl of one through four carbons; and

R_4 is hydrogen or alkyl of one through twelve carbons

with the limitation that when X is hydrogen at least one of R_1, R_2 and R_3 must be alkyl of one through six carbons.

References Cited

Jefferies, J.: Australian Chem. Soc. p. 527 (1962).

LORRAINE A. WEINBERGER, Primary Examiner

R. GERSTL, Assistant Examiner

U.S. Cl. X.R.

260—294, 294.3, 326.3, 343.2, 469, 479, 500.5, 515, 520, 544, 558, 559, 599, 600, 618 619; 424—299, 317, 341

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UNITED STATES PATENT OFFICE
CERTIFICATE OF CORRECTION

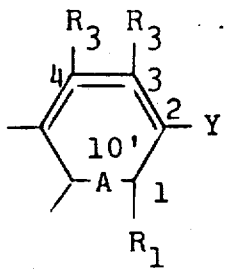
Patent No. 3,565,944 Dated February 23, 1971

Inventor(s) Kyu Tai Lee and Joel G. Whitney

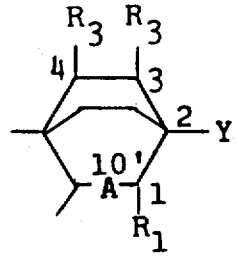
It is certified that error appears in the above-identified patent and that said Letters Patent are hereby corrected as shown below:

In Claim 1, on the sixteenth line, after the word "and", and prior to the reference character "R_5", insert the express: -- Y is $COOR_5$, where -- .

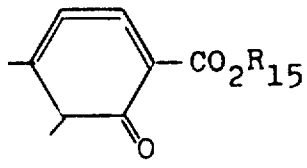
In Formula I, correct the right hand portion (the bicyclo-octane ring) from



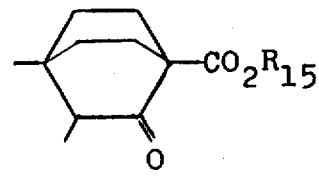
to



In Formula III, correct the right hand portion (the bicyclooctane ring) from

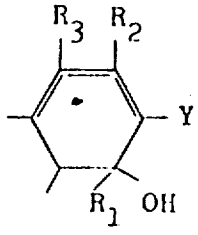


to

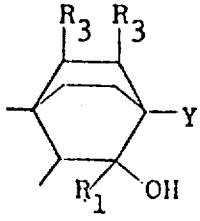


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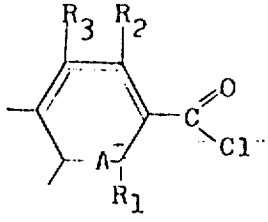
In Formula IV, correct the right hand portion (the bicyclooctane ring) from



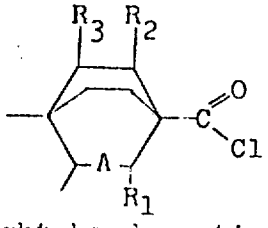
to



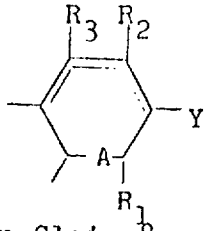
In Formula V, correct the right hand portion (the bicyclooctane ring) from



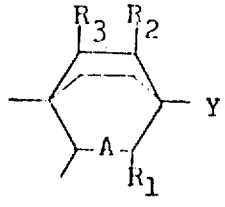
to



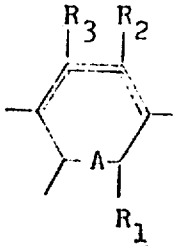
In Claim 1, correct the right hand portion of the formula (the bicyclooctane ring) from



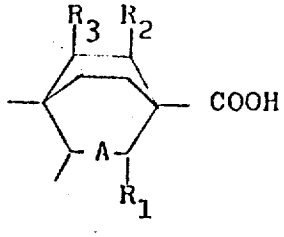
to



In Claim 8, correct the right hand portion of the formula (the bicyclooctane ring) from



to



Signed and sealed this 13th day of July 1971.

(SEAL)
Attest:

EDWARD M.FLETCHER,JR.
Attesting Officer

WILLIAM E. SCHUYLER, JR.
Commissioner of Patents