

PATENT SPECIFICATION

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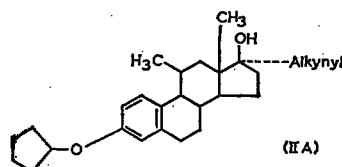
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(54) 11 β ,13 β -DIALKYLGONA-1,3,5(10)-TRIEN-3-OL 3-CYCLOALKYL ETHERS

- (71) We, G. D. SEARLE & Co., a Corporation organised and existing under the laws of the State of Delaware, United States of America, of Post Office Box 5110, Chicago, Illinois, U.S.A., do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—
 5 The present invention relates to a group of novel steroids represented by the general formula:

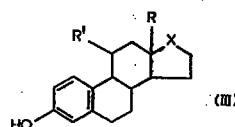
R'' is a methyl or ethyl radical, and n and X are as defined above, and also particularly preferred are those of the formula:



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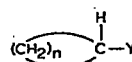
An especially preferred species of this invention is 17 α - ethynyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether.

The compounds of the present invention are conveniently prepared by etherification, in a conventional manner, of the 3 - hydroxy group of the corresponding compounds of the general formula::



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wherein R, R' and X are defined as before. Thus, a compound of formula (III) above is contacted with an etherifying agent of the type:



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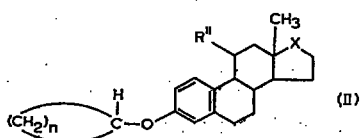
wherein

n is defined as above, and Y is halogen or a methane sulphonyloxy or toluene sulphonyloxy radical, in the presence of an appropriate acid accep-

55

- wherein
 15 R and R' are straight or branched-chain alkyl radicals containing from 1 to 7 carbon atoms, n is 4 or 5, and
 20 X is carbonyl or α - alkyne - β - hydroxy-methylene wherein the alkyne portion may be straight or branched-chained and contains 2 to 7 carbon atoms.
 The cycloalkyl radicals denoted by the

- 25 term may be cyclopentyl or cyclohexyl.
 Preferred compounds within the scope of formula (I) above are those compounds of the formula:



- 30 wherein
 [Price 25p]

Price 33p

tor to afford the corresponding cycloalkyl ether of formula (I). Cycloalkyl halides are particularly preferred etherifying agents. Suitable acid acceptors include alkaline carbonates (for example potassium carbonate) and alkaline alcoholates (for example sodium ethylate). The reaction is most preferably conducted under anhydrous conditions, and at elevated temperatures, with reflux temperature being generally preferred. Suitable solvents for carrying out the above reaction would be apparent to a person skilled in the art of organic chemistry. Preferred solvents include lower alkanols, for example ethanol.

15 A highly desirable alternative process for the production of the compounds of formula (I) wherein X is α - alkynyl - β - hydroxymethylene involves alkynylation, in a known manner, of the corresponding compounds of formula (I) wherein X is carbonyl. Thus, a 17-keto compound of formula (I) is contacted with a suitable alkynylating agent followed by, if necessary, decomposition of the resulting organometallic addition product, to afford the corresponding 17 α - alkynyl - 17 β - hydroxy compound of formula (I). The term "suitable alkynylating agent" refers to those organometallic reagents capable of reacting with a carbonyl grouping to form the organometallic addition product thereof. These organometallic reagents include alkynyl magnesium halides and alkynyl zinc halides, used under the conditions of the Grignard reaction, and also alkynyl lithiums, alkynyl sodiums, and alkynyl potassiums. A particularly preferred alkynylating agent is alkynyl lithium, suitably used in the form of an ethylene diamine complex. However, it is apparent that the aforementioned alkali metal salts of alkynes could instead be used in the presence of a strong base. Such bases include alkaline hydroxides (e.g. potassium hydroxide) and alkaline alkoxides (e.g. potassium tertiary butoxide). Suitable solvents for the alkynylation reaction include tetrahydrofuran, ether, glycol ethers and dioxane, the solvent of choice obviously depending upon the particular reagents employed. The alkynylation reaction is preferably carried out at temperatures of 20°C or less, an optimum temperature range between 0 to -10°C.

The compounds of this invention are useful as chemosterilants for the control of nuisance animal populations. Thus, these compounds provide a means for limiting the population of animals which are regarded as pests in various geographic areas of the world. Such nuisance animals, particularly when occurring in large numbers, can present severe economic and health hazards by damaging agricultural crops and trees, household articles and food-stuffs; by killing livestock or desirable wild animals and birds; by competing with more desirable animals for food; by destruction resulting from their burrowing and gnawing;

or by transmitting diseases to man and animals. These nuisance animals include opossums of the family *Didelphidae*, order *Marsupialia*; fruit-eating bats and true vampire bats of the order *Chiroptera*; rabbits and hares of the order *Lagomorpha*; members of the order *Carnivora* such as coyotes, blackbacked jackals, foxes, wolves, tayras, grisons, honey badgers, American badgers, mongooses and pumas; certain species of ungulates of the family *Suidae*; and most particularly, mammals of the order *Rodentia*, for example ground and tree squirrels, marmots, prairie "dogs" pocket gophers, tuzas and taltuzas, rice rats, highland desert mice, marsh rats, cotton rats, common hamsters, true lemmings, muskrats, gerbils, mole rats, garden dormice, tree dormice, spiny dormice, porcupines, caviars, guinea pigs, nutrias, cane rats, blesmols, sand rats, members of the genus *Microtus* such as meadow mice, and rodents of the family *Muridae* such as those of the genera *Apodemus*, *Millardia*, *Rattus* (especially black rats and norway rats), *Mus* (e.g. common house mice), *Bandicota* and *Nesokia*.

Representative of the chemosterilant activity of the novel compounds of this invention is their inhibition of the secretion of pituitary gonadotrophins and consequent inhibition of ovulation and conception in nuisance animals such as rats. Furthermore, these compounds have been found to prevent implantation in newly-mated rodents. In fact, a single dose of 0.005 mg of the representative species 17 α - ethynyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether has been found to be sufficient to interrupt early pregnancy in rats. In addition, fed to rats near the time of parturition, these compounds are excreted in the milk in sufficient quantities to sterilize the nursing female offspring. Such female rodents, when mature, exhibit nearly constant estrus but do not ovulate. Furthermore, because wild rodents, as well as other nuisance animals, cannot be expected to return with regularity to a single food source, a particularly important advantage of the instant compounds is their long duration of activity upon oral administration. Because of these facts, the compounds of this invention may be used as population control agents for nuisance animals, conveniently by placing them in a bait. The bait comprises one of the compounds of the instant invention and an edible carrier. The term "edible carrier" signifies all non-toxic substances consumable or ingestible by animals in solid, liquid or other suitable form. The edible carrier can thus, for example, consist of one or more of the following: foods, food additives (e.g. sweetening or flavouring agents), aerosol propellants, fillers, binders, common organic and inorganic solvents. When the carrier is a liquid, the bait can be in the form

of a solution, suspension, syrup or emulsion. The active ingredient, i.e. one of the compounds of this invention, and the carrier are mixed in a known manner and the bait so prepared is distributed in an area frequented by nuisance animals. Obviously, the bait can itself represent a substitute or supplemental food or drinking supply for the animals, or it can be in a form which is to be applied, for example, by spraying or injection, to the crops, trees or articles which the nuisance animals consume or ingest.

For rodents, the edible carrier is preferably a food which rodents find to be highly palatable, such as cereal grains, cracked corn, corn meal, bread crumbs, meat or fish scraps, oils such as vegetable or fish oils, powdered sugar, molasses, salt and spices, and various mixtures thereof. The bait so prepared is distributed in an area frequented by rodents. For greatest effect on total population, it is desirable to administer the material at about the time of parturition so that the female young will be sterilized. Thus, single distributions of bait at repeated intervals of 6 weeks are preferred for many rodent species. Obviously, the time interval will vary according to the reproductive cycle of the particular nuisance animal involved. The representative compound 17 α - ethynyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether can be distributed to rodents in this manner, preferably at a concentration of approximately 0.1 mg. per gram of dry bait, although the concentration of active ingredient can typically vary from approximately 0.02 mg to about 1.0 mg per gram of dry bait. However, it is apparent that the concentration of active ingredient can vary considerably from the amounts given above, depending upon the particular nuisance animal concerned and the specific edible carrier used.

The novel compounds of this invention, by virtue of the 11 β - alkyl substituent and the cycloalkyl group attached to the 3-position, are unusually potent estrogenic substances and display the further advantage of having a prolonged duration of activity. These compounds are thus useful as ingredients in compositions adapted for purposes necessitating the use of a potent estrogen. The instant compounds are also potent pituitary inhibitors. These compounds are, furthermore, potent both by injection and by oral administration.

The estrogenic property of the compounds of the invention is illustrated by the activity of a representative compound of this invention, namely 17 α - ethynyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether, when assayed by the following procedure.

The method used is adapted from that described by Peterson *et al.*, *J. Endocrinology*, 29, 255 (1964). This test depends upon the fact that the removal of one ovary from young

rats causes a stimulation of pituitary gonadotrophin secretion and a resultant hypertrophy of the remaining ovary. This test thus serves to measure the inhibition of pituitary gonadotrophin secretion.

According to this method, the test compound is dissolved or suspended in corn oil and administered buccally to a group of 72-day old female rats for 14 days beginning on the day of hemi-castration. On the day following the last injection, the animals are sacrificed and the remaining ovary is removed, cleaned of extraneous tissue, and weighed. A group of control animals is treated with corn oil alone. The degree of inhibition is calculated from the difference in ovarian weights between the treated and control animals. Compounds are considered active if they produce a significant decrease ($P < 0.05$) in ovarian weight as determined from the Wilcoxon Rank Sum Test. Ovarian weight responses are converted to percentage values, calculated according to the following formula:

$$\text{Per cent decrease in ovarian weight} = \frac{[(C-T)/(C-K)] \times 1000,}{}$$

where C equals the mean weight of the left ovary from current corn oil-treated hemicastrated control rats; T equals the mean weight of the left ovary from the treated group of animals; and K equals 35.4, a constant, which is the mean weight of left ovaries accumulated from a large number of 72-day old intact rats treated with corn oil.

On the basis, the ovarian weight of the intact controls (K) represents a value that would indicate 100% inhibition of the hypertrophy shown by the current hemicastrated controls. This latter group is assigned a value of 0%. Using these percentage values as the response, the potency of a compound relative to estrone is estimated. In this way, it has been found that a representative compound of this invention, i.e. 17 α - ethynyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether, has a potency of approximately 7200% relative to estrone. A structurally related known estrogen, namely 17 α - ethynylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether (described in United States Patent No. 3,159,543), possesses a potency of approximately 380% that of estrone in this same test.

Evidence of the pituitary-inhibiting property of the instant compounds is provided by the following test.

Young adult rats weighing about 200 to 250 grams are ovariectomized, then treated daily for 30 days, starting on the day of the operation, with a corn oil solution or suspension of the test compound. The animals are sacrificed on the day following the last treatment and the pituitary glands are removed for follicle stimulating hormone assay.

The follicle stimulating hormone assay is a modification of the ovarian augmentation test described by Steelman and Pohley, *Endocrinology*, 543, 604 (1953). In this test, a group of four 23-day old female rats is injected twice daily for 3 days with aliquot portions of saline extracts of the pituitaries taken from the donor animals. A similar group of control animals is treated with a standard follicle stimulating hormone preparation. Human chorionic gonadotrophin in the total amount of 50 I.U. per animal is administered to each group in order to augment the ovarian response and to mask any effects of lutenising hormone which may be present in the extracts. The combined weight of both the ovaries taken on the day after the last injection serves as the index of response. Follicle stimulating hormone potencies are calculated from response curves for the standard and pituitary extracts. The pituitary content of follicle stimulating hormone is then plotted against the dose of the compound and compared to the dose response line for estrone. The potency is thus expressed as a percentage of estrone. This test depends upon the fact that ovariectomy results in an increase in pituitary follicle stimulating hormone which reaches a plateau in 4 weeks and remains at a high level thereafter. The ability of a compound to inhibit this increase in follicle stimulating hormone following ovariectomy is determined by comparison of dose response curves of the compound with the standard, estrone. When tested in this manner, a representative species of this invention, 17α - ethynyl - 11β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether, was found to have a subcutaneous potency of 8300 per cent, and an oral potency of 1500 per cent; while the subcutaneous and oral potencies of the prior art estrogen, 17α - ethynylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether were found to be only 500 per cent and 300 per cent, respectively.

The potent estrogens of this invention can be administered also in conjunction with other potent hormonal agents, e.g. androgens or progestins, for uses which involve the need for such combinations, e.g. inhibition of ovulation.

The invention is illustrated by the following Examples, in which quantities of materials are indicated in parts by weight, and temperatures are indicated in degrees Centigrade ($^{\circ}\text{C}$). Nuclear magnetic resonance spectra were determined on a 60 mega Hertz instrument using tetramethyl silane as an internal reference, and are indicated in Hertz (cycles per second). Infra-red absorption are given in microns (μ).

EXAMPLE 1

To a solution of 5 parts of 3 - hydroxy - 11β - methylestra - 1,3,5(10) - trien - 17 -

one in 120 parts of ethanol were added successively 15 parts of anhydrous potassium carbonate and a solution of 5 parts of cyclopentyl iodide in 40 parts of ethanol. The resulting reaction mixture was heated and stirred at the reflux temperature in a nitrogen atmosphere for about 4 hours, at the end of which time another portion of 5 parts of cyclopentyl iodide dissolved in 40 parts of ethanol was added. Heating and stirring were continued for an additional 4 hours and the inorganic salts were then removed by filtration. Concentration of the solution by distillation under reduced pressure afforded a residual material, which was dissolved in approximately 1000 parts of ethyl acetate. The resulting organic solution was washed with water until neutral, then dried over anhydrous sodium sulphate and concentrated under reduced pressure until the product began to crystallise. At the end of that time, the solution was allowed to stand in order to permit completion of crystallisation. The resulting product was collected by filtration and dried, thus affording 3 - cyclopentyloxy - 11β - methylestra - 1,3,5(10) - trien - 17 - one, melting at 209 to 211.5 $^{\circ}\text{C}$. That compound exhibits characteristic nuclear magnetic resonance peaks, in deuterochloroform, at 51, 57, 62 and 284 Hertz (cycles per second).

By substituting an equivalent quantity of cyclohexyl iodide and otherwise proceeding according to the process described above, there was produced 3 - cyclohexyloxy - 11β - methylestra - 1,3,5(10) - trien - 17 - one. That compound exhibits characteristic nuclear magnetic resonance peaks at 50, 57.5 and 61 Hertz (cycles per second) in deuterochloroform, and is further characterised by an infra-red absorption maximum, in chloroform at 5.76 μ .

In a similar manner, substitution of an equivalent quantity of 17α - ethynyl - 11β - methylestra - 1,3,5(10) - triene - 3,17 β - diol into the procedure of the first paragraph of this example afforded 17α - ethynyl - 11β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether. That product exhibits characteristic nuclear magnetic resonance peaks in deuterochloroform, at 50, 57, 61, 157 and 283 Hertz (cycles per second).

In like manner, substitution of an equivalent quantity of 3 - hydroxy - 11β - ethylestra - 1,3,5(10) - trien - 17 - one into the procedure detailed in the first paragraph of this example, afforded 3 - cyclopentyloxy - 11β - ethylestra - 1,3,5(10) - trien - 17 - one. That compound is characterised by an infra-red absorption maximum in chloroform at 5.75 μ .

EXAMPLE 2

A suspension of 10 parts of the 30% lithium acetylide 70% ethylene diamine complex with 112 parts of tetrahydrofuran in a

nitrogen atmosphere was cooled to 0°C. by means of an ice bath. To that mixture was then added, with stirring over a period of about 20 minutes, a solution of 2.8 parts of 3 - cyclopentyloxy - 11β - methylestra - 1,3,5(10) - trien - 17 - one in 54 parts of tetrahydrofuran. The reaction mixture was placed under an atmosphere of acetylene and stirred at approximately 0°C for about 3 hours. Decomposition of the reaction mixture by careful addition of water resulted in precipitation of the lithium salts as a gummy mass. The organic solution was separated by decantation and the inorganic salts were washed with fresh tetrahydrofuran. The tetrahydrofuran solutions were combined and concentrated to dryness under reduced pressure. The resulting residue was dissolved in ether and the ether solution was washed with water until neutral, then dried over anhydrous sodium sulphate and concentrated to dryness under reduced pressure, thus affording 17α - ethynyl - 11β - methylestra - 1,3,5(10) - triene - 3,17β - diol 3 - cyclopentyl ether as an amorphous powder. This product exhibits characteristic resonance peaks, in deuteriochloroform, at 50, 57, 61, 157 and 283 Hertz (cycles per second).

When an equivalent quantity of lithium propynylide was substituted into the above procedure there was obtained 17α - propynyl - 11β - methylestra - 1,3,5(10) - triene - 3,17β - diol 3 - cyclopentyl ether. That product exhibits characteristic nuclear magnetic resonance peaks, in deuteriochloroform, at 50, 58, 112.5 and 284 Hertz (cycles per second).

By substituting an equivalent quantity of 3 - cyclohexyloxy - 11β - methylestra - 1,3,5(10) - trien - 17 - one and otherwise proceeding according to the process of the first paragraph of this example, there was produced 17α - ethynyl - 11β - methylestra - 1,3,5(10) - triene - 3,17β - diol 3 - cyclohexyl ether. That compound exhibits characteristic nuclear magnetic resonance peaks, in deuteriochloroform, at 50.5, 57.5 and 156 Hertz (cycles per second), and is further characterised by an infra-red absorption maximum, in chloroform, at 2.75 μ.

Similarly, substitution of an equivalent quantity of 3 - cyclopentyloxy - 11β - ethylestra - 1,3,5(10) - trien - 17 - one in the procedure detailed in the first paragraph of this example afforded 17α - ethynyl - 11β - ethylestra - 1,3,5(10) - triene - 3,17β - diol 3 - cyclopentyl ether. That compound exhibits characteristic nuclear magnetic resonance peaks, in deuteriochloroform, at 156.5 and 283 Hertz (cycles per second) and is further characterised by an infra-red absorption maximum, in chloroform, at 2.76 μ.

EXAMPLE 3

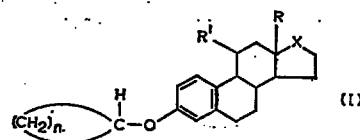
3150 Parts of ethyl cellulose having a viscosity of about 10 centipoises were dissolved

in 60,000 parts of methanol with stirring. To that solution was added, with stirring, a solution of about 54.4 parts of 17α - ethynyl - 11β - methylestra - 1,3,5(10) - triene - 3,17β - diol 3 - cyclopentyl ether in approximately 12,000 parts of methanol. To the resultant mixture were then added slowly 630 parts of zein and 200 parts of glycerol, followed by approximately 3600 parts of methanol.

About 90,000 parts of the above solution were sprayed on to 450,000 parts of cracked corn. The sprayed corn was then dried thoroughly in a coating pan, thus affording a dry bait suitable for controlling the population of nuisance animals such as rodents.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:



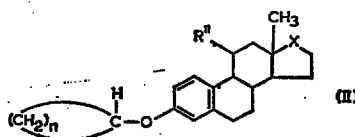
wherein

R and R' are straight or branched-chain alkyl radicals containing 1 to 7 carbon atoms,

n is 4 or 5, and

X is carbonyl or α - alkynyl - β - hydroxymethylene wherein the alkynyl portion is straight or branched-chain and contains 2 to 7 carbon atoms.

2. Compounds of the general formula:



wherein

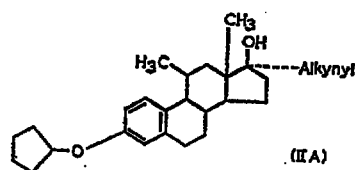
R'' is a methyl or ethyl radical,

n is 4 or 5, and

X is carbonyl or α - alkynyl - β - hydroxymethylene wherein the alkynyl portion is straight or branched-chain and contains 2 to 7 carbon atoms.

3. Cyclopentyloxy - 11β - methylestra - 1,3,5(10) - trien - 17 - one.

4. Compounds of the general formula:





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nitrogen atmosphere was cooled to 0°C. by means of an ice bath. To that mixture was then added, with stirring over a period of about 20 minutes, a solution of 2.8 parts of 3 - cyclopentyloxy - 11β - methylestra - 1,3,5(10) - trien - 17 - one in 54 parts of tetrahydrofuran. The reaction mixture was placed under an atmosphere of acetylene and stirred at approximately 0°C for about 3 hours. Decomposition of the reaction mixture by careful addition of water resulted in precipitation of the lithium salts as a gummy mass. The organic solution was separated by decantation and the inorganic salts were washed with fresh tetrahydrofuran. The tetrahydrofuran solutions were combined and concentrated to dryness under reduced pressure. The resulting residue was dissolved in ether and the ether solution was washed with water until neutral, then dried over anhydrous sodium sulphate and concentrated to dryness under reduced pressure, thus affording 17α - ethynyl - 11β - methylestra - 1,3,5(10) - triene - 3,17β - diol 3 - cyclopentyl ether as an amorphous powder. This product exhibits characteristic resonance peaks, in deuteriochloroform, at 50, 57, 61, 157 and 283 Hertz (cycles per second).

When an equivalent quantity of lithium propynylide was substituted into the above procedure there was obtained 17α - propynyl - 11β - methylestra - 1,3,5(10) - triene - 3,17β - diol 3 - cyclopentyl ether. That product exhibits characteristic nuclear magnetic resonance peaks, in deuteriochloroform, at 50, 58, 112.5 and 284 Hertz (cycles per second).

By substituting an equivalent quantity of 3 - cyclohexyloxy - 11β - methylestra - 1,3,5(10) - trien - 17 - one and otherwise proceeding according to the process of the first paragraph of this example, there was produced 17α - ethynyl - 11β - methylestra - 1,3,5(10) - triene - 3,17β - diol 3 - cyclohexyl ether. That compound exhibits characteristic nuclear magnetic resonance peaks, in deuteriochloroform, at 50.5, 57.5 and 156 Hertz (cycles per second), and is further characterized by an infra-red absorption maximum, in chloroform, at 2.75 μ.

Similarly, substitution of an equivalent quantity of 3 - cyclopentyloxy - 11β - ethylestra - 1,3,5(10) - trien - 17 - one in the procedure detailed in the first paragraph of this example afforded 17α - ethynyl - 11β - ethylestra - 1,3,5(10) - triene - 3,17β - diol 3 - cyclopentyl ether. That compound exhibits characteristic nuclear magnetic resonance peaks, in deuteriochloroform, at 156.5 and 283 Hertz (cycles per second) and is further characterized by an infra-red absorption maximum, in chloroform, at 2.76 μ.

EXAMPLE 3

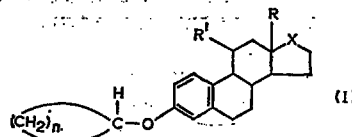
3150 Parts of ethyl cellulose having a viscosity of about 10 centipoises were dissolved

in 60,000 parts of methanol with stirring. To that solution was added, with stirring, a solution of about 54.4 parts of 17α - ethynyl - 11β - methylestra - 1,3,5(10) - triene - 3,17β - diol 3 - cyclopentyl ether in approximately 12,000 parts of methanol. To the resultant mixture were then added slowly 630 parts of zein and 200 parts of glycerol, followed by approximately 3600 parts of methanol.

About 90,000 parts of the above solution were sprayed on to 450,000 parts of cracked corn. The sprayed corn was then dried thoroughly in a coating pan, thus affording a dry bait suitable for controlling the population of nuisance animals such as rodents.

WHAT WE CLAIM IS:—

1. Compounds of the general formula:



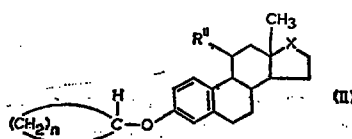
wherein

R and R' are straight or branched-chain alkyl radicals containing 1 to 7 carbon atoms,

n is 4 or 5, and

X is carbonyl or α - alkynyl - β - hydroxymethylene wherein the alkynyl portion is straight or branched-chain and contains 2 to 7 carbon atoms.

2. Compounds of the general formula:



wherein

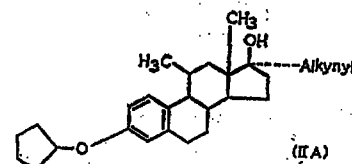
R'' is a methyl or ethyl radical,

n is 4 or 5, and

X is carbonyl or α - alkynyl - β - hydroxymethylene wherein the alkynyl portion is straight or branched-chain and contains 2 to 7 carbon atoms.

3. Cyclopentyloxy - 11β - methylestra - 1,3,5(10) - trien - 17 - one.

4. Compounds of the general formula:



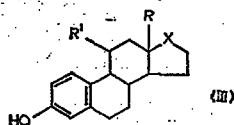


wherein the alkynyl radical is straight or branched-chain and contains 2 to 7 carbon atoms.

5. 17 α - Ethynyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether.

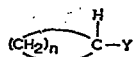
6. A process for the preparation of compounds as claimed in claim 1 which comprises:

- 10 (a) etherification of the 3 - hydroxy group of a compound of the general formula:



wherein R, R' and X are defined as above, with an etherifying agent of the type:

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wherein

n is as defined above, and

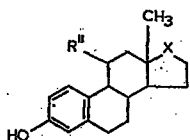
Y is halogen or a methane sulphonyloxy or toluene sulphonyloxy radical,

- 20 in the presence of an appropriate acid acceptor, to afford the corresponding compound of formula (I) above; or

- (b) alkynylation of a compound of formula (I) wherein X is carbonyl, to afford the corresponding compound of formula (I) wherein X is α - alkynyl - β - hydroxymethylene.

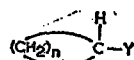
- 25 7. A process for the preparation of compounds as claimed in 2 which comprises:

- 30 (a) etherification of the 3 - hydroxy group of a compound of the general formula:



wherein R'' and X are defined as above, with an etherifying agent of the type:

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wherein

n is defined as above, and

Y is halogen or a methane sulphonyloxy or toluene sulphonyloxy radical,

in the presence of an appropriate acid acceptor, to afford the corresponding compound of formula II above; or

- (b) alkynylation of a compound of formula (II) wherein X is carbonyl, to afford the corresponding compound of formula (II) wherein X is α - alkynyl - β - hydroxymethylene.

8. A process according to claim 6(a) or 7(a) wherein the etherifying agent is a cycloalkyl halide.

9. A process according to claim 6(b) or 7(b) wherein the alkynylation is effected by use of an alkynyl lithium.

10. A process for the preparation of 3 - cyclopentyloxy - 11 β - methylestra - 1,3,5(10) - trien - 17 - one which comprises contacting 3 - hydroxy - 11 β - methyl - estra - 1,3,5(10) - trien - 17 - one with cyclopentyl iodide, in the presence of an appropriate acid acceptor.

11. A process for the preparation of 17 α - ethynyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether which comprises contacting 3 - cyclopentyloxy - 11 β - methylestra - 1,3,5(10) - trien - 17 - one with lithium acetylide in the form of its ethylene diamine complex.

12. A process for the preparation of 17 α - ethynyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether which comprises contacting 17 α - ethynyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol with cyclopentyl iodide, in the presence of an appropriate acid acceptor.

13. Compounds as claimed in claim 1 whenever prepared by a process as claimed in claim 6.

14. Compounds as claimed in claim 2 whenever prepared by a process as claimed in claim 7.

15. 3 - Cyclopentyloxy - 11 β - methylestra - 1,3,5(10) - trien - 17 - one, whenever prepared by the process of claim 10.

16. 17 α - Ethynyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether whenever prepared by the process of claim 11 or 12.

17. A bait for nuisance animal control which comprises a compound as claimed in claim 1 and an edible carrier.

18. A bait for nuisance animal control which comprises 17 α - ethynyl - 11 β - methylestra - 1,3,5(10) - triene 3,17 β - diol 3 - cyclopentyl ether and an edible carrier.

19. A method of preparing a bait for nuisance animal control which comprises mixing a compound as claimed in claim 1 with an edible carrier.

20. A method of preparing a bait for nuisance animal control which comprises mixing 17 α - ethynyl - 11 β - methylestra - 1,3,5(10) - triene - 3,17 β - diol 3 - cyclopentyl ether with an edible carrier.

21. A method of controlling nuisance animal populations which comprises administering to said nuisance animals a compound as claimed in claim 1.
- 5 22. A method of controlling nuisance animal populations which comprises administering to said nuisance animals the compound 17α - ethynyl - 11β - methylestra - $1,3,5(10)$ - triene - $3,17\beta$ - diol 3 - cyclopentyl ether.
- 10 23. A method of controlling nuisance animal populations which comprises administering to said nuisance animals a bait containing a compound as claimed in claim 1
- 15 and an edible carrier.
24. A method of controlling nuisance animal populations which comprises administering to said nuisance animals a bait containing 17α - ethynyl - 11β - methylestra - $1,3,5(10)$ - triene - $3,17\beta$ - diol 3 - cyclopentyl ether and an edible carrier. 20

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