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2,933,510

3-KETO-4-HALO- $\Delta^{4,5}$ STEROID

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17 Claims. (Cl. 260—397.3)

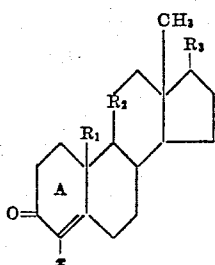
This invention relates to new steroid compounds and the method of preparing them. More particularly, it relates to certain physiologically active 3-keto-4-halo- $\Delta^{4,5}$ compounds and the method of preparing them. The invention provides 4-halo derivatives of active androgenic, anabolic, progestational and corticoid hormones.

The components of this invention have hormone activity and, more specifically, variously have advantageous anabolic, androgenic, progestational and cortical activity with minimal side effects. It is well known that the active steroid hormones normally exhibit a plurality of physiological effects and that subsidiary effects limit the clinical use of the hormones. It has been found that the compounds of this invention have an advantageous ratio of desirable to undesirable activity.

In addition, this invention provides a novel and inexpensive method for producing halogen derivatives of important steroids.

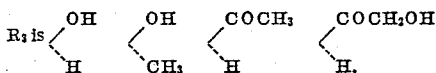
The compounds of this invention are 3-keto-4-halo- $\Delta^{4,5}$ steroids derived from 4-estrenes, 4-androstenes or 4-pregnenes. Advantageously the compounds of this invention have the following structure:

FORMULA 1

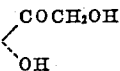


in which:

R_1 is hydrogen or methyl, R_2 is $\text{C}=\text{O}$, CH_2 or $\text{OH}-\text{C}-\text{H}$



or



and x is halogen, preferably chlorine or bromine.

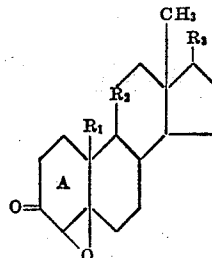
Aliphatic, aryl and aralkyl esters of the above compounds such as, for example, acetate, benzoate, propionate, phenylacetate and half-succinate esters are also included within the scope of this invention. Such esters may be obtained by utilizing the desired ester of the epoxy starting material or by the preferred method of reacting the 4-halo derivative with the desired acyl halide or anhydride in a tertiary amine such as pyridine.

The method in accordance with this invention comprises treating a 3-keto-4,5-epoxysteroid with a hydrohalic

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acid or the hydrohalic acid salt of a tertiary amine to obtain the corresponding 3-keto-4-halo- $\Delta^{4,5}$ steroid. The 3-keto-4,5-epoxysteroid has the following structural formula:

FORMULA 2



in which R_1 , R_2 and R_3 are as given above. It will be understood that the above structure includes the $4\alpha,5\alpha$ -epoxides and the $4\beta,5\beta$ -epoxides, the bonds indicated by the solid lines in the 4 and 5 positions and connected to the oxygen not specifically indicating the isomeric form but rather being intended to include both the alpha and beta forms in the formula as given above and where used hereinafter, including in the claims. Since it is known to the art that epoxy compounds react with a hydrohalic acid to give the related halohydrins, it is surprising that the method in accordance with this invention produces halogen-containing olefins under comparable conditions.

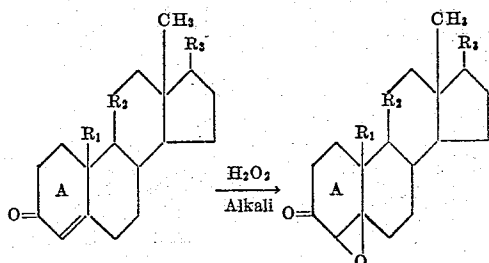
More specifically, the desired 4-halo end product can be obtained by treating a solution or suspension of the 4,5 epoxysteroid in a halogenated or oxygenated water immiscible solvent such as carbon tetrachloride, methylene chloride, chloroform or ether with hydrohalic acid such as, for example, hydrogen chloride or hydrogen bromide either as a solution in a solvent miscible with the solvent for the epoxy compound or as a gas bubbled through the reaction mixture. The solvent for the hydrohalic acid may be, for example, a ketone solvent such as acetone or a lower aliphatic alcohol such as methanol, ethanol or propanol. Alternatively, the epoxy compound may be dissolved in a water miscible solvent such as, for example, dioxane, acetic acid, propionic acid, acetone or ethanol and reacted with an aqueous or acetic acid solution of the hydrohalic acid. In the case of both methods it is preferred to maintain the temperature of the reaction fluid from about 0°C . to about 35°C . for from about 10 minutes to several days.

Where the hydrohalic acid salt of a tertiary aromatic amine is employed, a solution of the 4,5 epoxysteroid in a suitable solvent is heated at from about 60°C . to about 100°C . and preferably at reflux temperature for from about 2 to about 20 hours with a solution of the amine hydrohalide in a solvent miscible with the solvent for the epoxy compound. Exemplary of suitable solvents for both the epoxy compound and the amine hydrohalide are ethanol, chloroform, methanol, carbon tetrachloride, dioxane and dimethylformamide. The hydrohalide of a tertiary amine may be, for example, pyridine hydrobromide, collidine hydrochloride or α -picoline hydrobromide.

The 3-keto-4-halo- $\Delta^{4,5}$ steroid of this invention is obtained from the reaction mixture by use of ordinary isolation procedures well known to the art. Thus, for example, the reaction mass may be diluted with water and the 3-keto-4-halo- $\Delta^{4,5}$ compound extracted with a suitable solvent such as, for example, methylene chloride, benzene, chloroform or ether. The solvent extract is washed with water, dried and concentrated to a crystalline mass. If desired, the end product can be recrystallized from an alcohol such as, for example, ethanol or from a mixture of solvents, such as methylene chloride-pentane.

The epoxy starting materials of Formula 2 are readily

prepared by treating a 3-keto- Δ^4 -steroid compound of the 4-estrene, 4-androstene, or 4-pregnene series in a water miscible solvent with an alkaline hydrogen peroxide aqueous solution. This reaction is shown in the following scheme, in which R_1 , R_2 and R_3 are as given above:



The alkali used may be any alkali metal hydroxide or carbonate, such as, for example, sodium hydroxide, potassium hydroxide, sodium carbonate or potassium carbonate.

The water miscible solvent may be, for example, a lower aliphatic alcohol such as methanol or ethanol, a ketone solvent such as acetone and methyl ethyl ketone or dioxane. By way of further example solvent mixtures such as benzene or a chlorinated methane such as chloroform, carbon tetrachloride or methylene chloride in admixture with a major proportion of a lower aliphatic alcohol such as methanol or ethanol are satisfactory.

The reaction will be carried out at a low temperature, preferably from about -20°C . to about 30°C . and advantageously from about -20°C . to $+10^\circ\text{C}$.

The reaction is preferably carried out until the major proportion of the starting material has been epoxidized. Advantageously the course of the reaction will be checked spectrophotometrically and the reaction mixture quenched preferably with cold water immediately after the disappearance of unsaturation in ring A, which is indicated by the disappearance of the characteristic α,β -unsaturated ketone absorption in the $238\text{ m}\mu$ - $242\text{ m}\mu$ region. The quenching at this state of the reaction insures the avoidance of further undesired oxidation to acidic products. The desired 4,5-epoxy compounds are obtained by filtration or by solvent extraction.

The epoxy starting materials of Formula 2 and the method of their preparation are fully set forth in our copending patent application, Serial No. 486,014, filed February 3, 1955, the disclosure of which is incorporated herewith. Reference may be made to said application, Serial No. 486,014, for specific examples of said epoxy starting materials as well as for specific detail as to the method of their preparation.

The compounds of this invention and the method of their preparation will be more specifically illustrated by the following examples. Our copending patent application, Serial No. 486,014, specifically illustrates the preparation of the starting material used in each of the following examples.

Example I.—4-bromotestosterone

A solution of 0.5 g. of 4,5-epoxytestosterone, M.P. 138 - 140°C ., was dissolved in 5 ml. of glacial acetic acid and cooled to 15°C . One milliliter of 30% hydrogen bromide in acetic acid was added and the reaction kept at 10 - 15°C . for 30 minutes. The solution was poured with stirring into 200 ml. of water, and the precipitated solid was collected by filtration. The product, 4-bromotestosterone, M.P. 152 - 154°C . had an absorption maximum at $261\text{ m}\mu$ = $11,600$, and weighed 590 mg.

Example II.—4-bromotestosterone

When 0.5 g. of the isomeric 4,5-epoxytestosterone, M.P. 152 - 155°C ., was treated in the manner described in Example I, 0.58 g. of the identical 4-bromo-testosterone, M.P. 155 - 157°C ., E_{261} = $11,800$ was obtained. This

gave no depression when melted with the 4-bromotestosterone described in Example I.

Example III.—4-chlorotestosterone

To a solution of 1.0 g. of 4,5-epoxytestosterone (stereoisomeric mixture) in 10 ml. of glacial acetic acid was added 2 ml. of an 8% hydrogen chloride in acetic acid solution. The reaction was kept for 12 hours at room temperature, then diluted cautiously with water to induce crystallization. The precipitate was removed by filtration and dried yielding 1.04 g. of 4-chlorotestosterone, M.P. 210 - 218°C . Recrystallization from methylene chloride-pentane afforded glistening prisms, M.P. 215 - 222°C ., E_{253} = $11,600$.

Example IV.—4-bromoprogesterone

One gram of 4,5-epoxyprogesterone (stereoisomeric mixture) was dissolved in 10 ml. of glacial acetic acid and the solution cooled to 15°C . To the cooled solution, 1 ml. of a 30% hydrogen bromide in acetic acid solution was added, and the reaction kept at 15°C . for 20 minutes. The solution was poured into 200 ml. of water and the precipitated product collected by filtration. The product, 1.18 g. of 4-bromoprogesterone, was crystallized from methylene chloride-pentane to give glistening prisms, M.P. 170 - 172°C . dec., E_{263} = $9,000$.

Example V.—4-bromoprogesterone

One gram of 4,5-epoxyprogesterone (stereoisomeric mixture) was dissolved in 10 ml. of purified dioxane and 2 ml. of 48% hydrobromic acid were added. The reaction was kept at 25°C . for 36 hours with occasional swirling, then was diluted with 75 ml. of water. The precipitated solid was filtered and washed well with water. Crystallization from methylene chloride-ether afforded 0.7 g. of 4-bromoprogesterone, M.P. 178 - 180°C ., E_{261} = $10,000$, which gave no depression on melting with that of Example IV.

Example VI.—4-chloroprogesterone

To one gram of 4,5-epoxyprogesterone (stereoisomeric mixture) dissolved in 10 ml. of glacial acetic acid, 1 ml. of a 25% solution of hydrogen chloride in acetic acid was added. The reaction mixture was kept at room temperature for 15 hours, during which time crystals of 4-chloroprogesterone came out. The crystals, 410 mg., were collected by filtration. They melted at 205 - 213°C ., and had an absorption maximum at $255\text{ m}\mu$ = $13,000$. A second crop of material, 540 mg. melting at 209 - 215°C ., E_{255} = $11,000$ was obtained from the mother liquor.

Example VII.—4-bromodesoxycorticosterone

Three grams of 4,5-epoxydesoxycorticosterone (stereoisomeric mixture) and 5 g. of pyridine hydrobromide were refluxed for 2 hours in 50 ml. of anhydrous ethanol. The solution was then concentrated to remove the solvent, diluted with water and extracted with methylene chloride. The methylene chloride extract was washed with water, dried and concentrated to a crystalline mass. Upon recrystallization from ethanol, 4-bromodesoxycorticosterone, M.P. 173 - 175°C ., $E_{261}\text{ m}\mu$ = $12,200$.

Example VIII.—4-bromocortisone

A solution of 1.0 g. of cortisone oxide (stereoisomeric mixture) in 10 ml. of methylene chloride was cooled to 5°C ., and 2 ml. of 30% hydrogen bromide in acetic acid was added. The reaction was held at 5 - 10°C . for 30 minutes; then was poured into 100 ml. of water and extracted with additional methylene chloride. The methylene chloride extract was washed free of acid and dried. Removal of solvent afforded 4-bromocortisone as a pale yellow fluff, E_{263} = $8,300$.

Example IX.—4-bromohydrocortisone

A solution of 1 g. of 4,5-epoxyhydrocortisone (stereo-

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isomeric mixture) in 10 ml. of chloroform was cooled to 5° C. and treated for 30 minutes at 5–10° C. with 2 ml. of 30% hydrogen bromide in acetic acid. Upon working up the reaction, 4-bromohydrocortisone was obtained as a yellow fluff, $E_{263} m\mu=9,000$.

Example X.—4-bromo-19-nortestosterone

One gram of 4,5-epoxy-19-nortestosterone was dissolved in 10 ml. of glacial acetic acid and the solution cooled to 15° C. One ml. of a 30% hydrogen bromide in acetic acid solution was added and the solution kept at 15° C. for one hour. Dilution with water afforded a precipitate which was extracted with benzene, washed with water and dried. The benzene extract upon concentration yielded 100 mg. of 4-bromo-19-nortestosterone, M.P. 125–128° C., dec., $E_{262} m\mu=8,000$.

Example XI.—4-bromo-19-nortestosterone benzoate

A solution of 1.5 g. of 4,5-epoxy-19-nortestosterone benzoate (stereoisomeric mixture) in 20 ml. of acetic acid was cooled in an ice bath and treated with 2 ml. of 27% hydrogen bromide in acetic acid for 20 minutes. The reaction was diluted with water and the bromo compound extracted with methylene chloride. The methylene chloride extract was washed with water, sodium bicarbonate solution and water. The solution was concentrated in vacuo and the product crystallized from ether. The yield of product, M.P. 118–122° C. dec., $E_{262} m\mu=13,000$ was 1.35 g.

Example XII.—4-bromo-19-nortestosterone benzoate

One gram of crude 4,5-epoxy-18-nortestosterone benzoate (stereoisomeric mixture) was dissolved in 15 ml. of anhydrous ether, cooled, and stirred for 20 minutes with 2 ml. of 27% hydrogen bromide in acetic acid. Upon working up as described in the previous example, 420 mg. of 4-bromo-19-nortestosterone benzoate, M.P. 118–120° C. dec., $E_{262} m\mu=12,000$ was obtained.

Example XIII.—4-bromo-17 α -methyltestosterone

A solution of 4 g. of 4,5-epoxy-17 α -methyltestosterone (stereoisomeric mixture) in 50 ml. of glacial acetic acid was cooled in an ice bath. A saturated solution of hydrogen chloride in glacial acetic acid was added. The mixture was allowed to come to room temperature and to stand for 24 hours with occasional swirling. The desired 4-bromo-17 α -methyltestosterone was isolated by quenching in water, filtering and washing well with water. A characteristic unsaturated ketone absorption on the crude product was observed spectrophotometrically.

Example XIV.—4-chlorotestosterone-17-acetate

A solution of 1.2 g. of 4,5-epoxytestosterone-17-acetate, M.P. 132–135° C., in 40 ml. of dimethylformamide was mixed with a solution of one equivalent of collidine hydrochloride in 5 ml. of dimethylformamide. The reaction mixture was heated at 80 to 90° C. for ten hours. After quenching in water, extracting with chloroform and washing with water and dilute acid, the desired crude compound as indicated by ultraviolet absorption was obtained.

Example XV

One gram of 4-bromotestosterone in 4 ml. of pyridine was reacted with 0.3 g. of succinic anhydride at room temperature for two days. The reaction mixture was quenched carefully with water to separate the desired 17-succinate half ester after washing well with water and air drying. A satisfactory E_1' was noted on the ultraviolet spectrum.

Example XVI.—4-bromotestosterone

A solution of 0.5 g. of 4,5-epoxytestosterone (stereoisomeric mixture) in dry ether was saturated with hydrogen bromide gas several times over a period of twelve hours at room temperature. The excess acid was removed from

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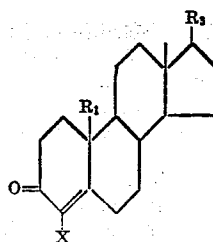
the reaction mixture by washing with carbonate solution. The ether was dried and evaporated in vacuo, yielding 500 mg. of crude 4-bromotestosterone.

It is not desired to be limited except as set forth in the following claims.

This application is a continuation-in-part of our application, Serial No. 486,014, filed February 3, 1955, now abandoned.

What is claimed is:

1. A compound having the following basic structural formula:



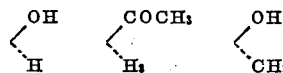
wherein X is a member selected from the group consisting of bromo and chloro; R₁ is a member selected from the group consisting of hydrogen and methyl; when R₁ is hydrogen R₂ is a member selected from the group consisting of



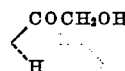
and



and when R₁ is methyl R₂ is a member selected from the group consisting of

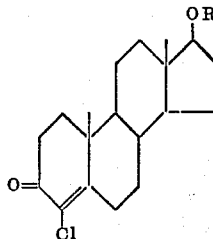


and



2. 4-chloroprogestosterone.

3. A compound having the formula



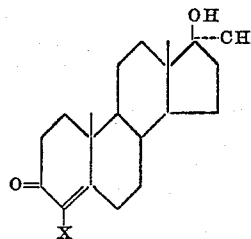
wherein R is selected from the group consisting of hydrogen and acyl.

4. 4-chlorotestosterone-17-acetate.

5. 4-chlorotestosterone.

6. 4-bromotestosterone.

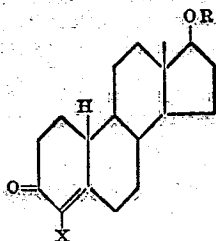
7. A compound having the formula



wherein X is a member selected from the group consisting of bromo and chloro.

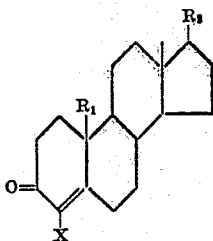
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8. 4-bromo-17 α -methyltestosterone.
9. A compound having the formula



wherein X is a member selected from the group consisting of bromo and chloro and R is selected from the group consisting of hydrogen and acyl.

10. 4-bromo-19-nortestosterone.
11. 4-bromo-19-nortestosterone benzoate.
12. 4-bromocortisone.
13. 4-bromohydrocortisone.
14. 4-bromodesoxycorticosterone.
15. The process of preparing a steroid having the following structural formula:



wherein X is a member selected from the group consisting of bromo and chloro; R₁ is a member selected from the group consisting of hydrogen and methyl; when R₁ is hydrogen R₂ is a member selected from the group consisting of

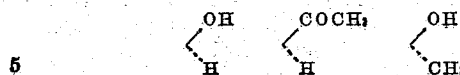


and



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and when R₁ is methyl R₂ is a member selected from the group consisting of



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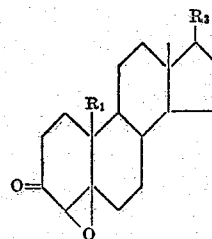
and



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which comprises reacting a 3-keto-4,5-epoxy steroid having the following formula:

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wherein R₁ and R₂ are as defined above, with a hydrohalic acid reagent selected from the group consisting of hydrobromic acid, hydrochloric acid, the hydrochloride of a tertiary aromatic amine and the hydrobromide of a tertiary aromatic amine.

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16. The process of claim 15 in which the epoxy compound and the hydrohalic acid reagent are in mutually miscible solvents.

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17. The process of claim 16 in which the reaction is carried out at a temperature in the range of from about 0° C. to about 35° C.

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