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# UNITED STATES PATENT OFFICE

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## HALOSTEROIDS AND PREPARATION OF THE SAME

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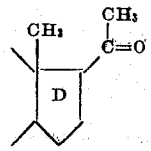
18 Claims. (Cl. 260—397.3)

This invention relates to halosteroids and preparation of the same.

More particularly this invention relates to halosteroids which are useful as intermediates for the preparation of androstane derivatives.

The terms androstane and pregnane as used in this specification and in the appended claims are to be understood as comprehending steroids of 19 and 21 carbon atoms respectively, regardless of the particular stereo-chemical configuration in the nucleus. For example, the term androstane compound is to be understood to include compounds having the "allo-" configuration at $C_5$ such as androsterone, or steroids having the "regular" configuration at $C_5$ such as etio-cholanol-3($\beta$)-one-17, as well as ring-unsaturated steroids such as testosterone.

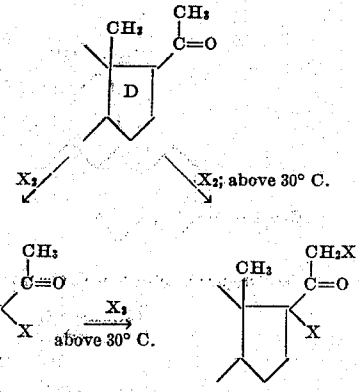
It has now been found that 20-keto-pregnane compounds having in ring D the structure




are surprisingly readily halogenated, that is to say, chlorinated or brominated. It has been found that this halogenation proceeds readily at moderate temperatures and indeed the first halogen atom, which becomes attached to C-17 can be introduced at room temperature. A second halogen atom, which becomes attached to C-21, can also be introduced at moderate temperatures, best above 30° C. Much higher temperatures than approximately 100° C. should be avoided because the new halosteroids are somewhat prone to thermal decomposition. It has also been found that the halogenation may be controlled to proceed stepwise, with intermediate formation of the 17-halo-20-keto-pregnane compound, or the two steps may be effected simultaneously, with direct production of the 17,21-dihalo-20-keto-pregnane compound.

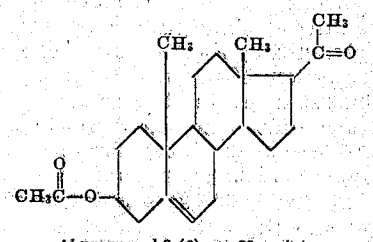
The halogenation is best conducted in the presence of a solvent inert to elementary chlorine or bromine. Such solvents include the liquid lower organic acids, such as acetic acid, propionic acid, etc., halohydrocarbons, such as carbon tetrachloride, chloroform, acetylene tetrachloride, ethylene dibromide, etc., as well as other inert solvents, such as nitrobenzene. While the use of a catalyst is not necessary, its use greatly facilitates the introduction of the second halogen atom. Suitable catalysts include mineral acids, such as hydrochloric acid and hydrobromic acid.

In general the halogenation of a 20-keto-pregnane compound proceeds as follows regardless of the nature of the substituents or groupings in rings A, B and C.



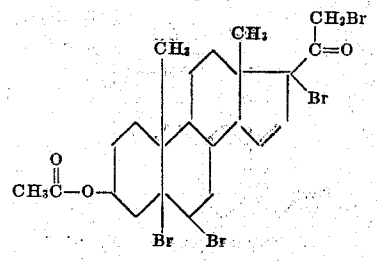

This does not imply, however, that rings A, B and C are necessarily unaffected during the halogenation, for if certain reactive groupings, such as carbon-to-carbon double bonds or ketone groupings, are present in rings A, B and C, the halogen may act at these points as well as on the structural grouping at ring D.

If a 20-keto-pregnane compound containing a carbon-to-carbon double bond in rings A, B or C is halogenated, the product will be found to have added halogen at the double bond as well as to have substituted halogen in the grouping attached to ring D. This may be illustrated as follows in the case of $\Delta^5$-pregnenol-3($\beta$)-one-20 acetate:




$\Delta^5$-pregnenol-3 ($\beta$)-one-20 acetate

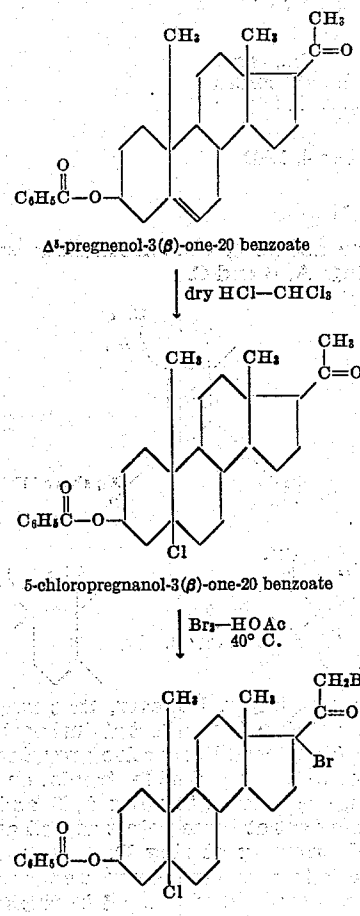
$Br_2$—HOAc
40° C.



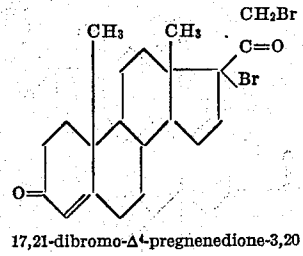

5, 6, 17, 21-tetrabromo-pregnanol-3($\beta$)-one-20 acetate

A variant of the above illustration consists first

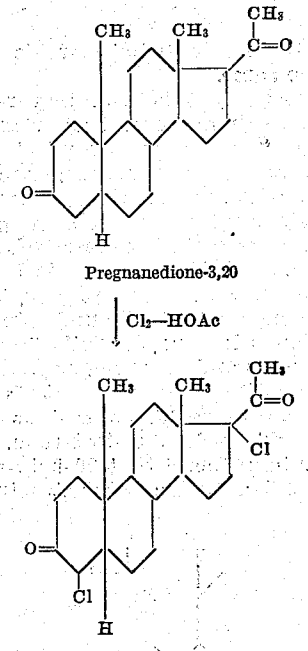
in saturating the ring double bond of the nuclearly unsaturated 20-keto-pregnane compound with halogen, or even with hydrogen halide, and then reacting with halogen, for example, as follows:




Since halogenation tends to occur at carbon-to-carbon double bonds in rings A, B and C at the same time that halogenation occurs at ring D, compounds which are halogenated at ring D and which also have a ring A, B or C double bond cannot be directly obtained by halogenation, but must be obtained by a combination of reactions. As an illustration, $\Delta^5$-pregnenol-3($\beta$)-one-20 can be brominated in an inert solvent such as carbon tetrachloride, the 5,6,17,21-tetrabromo-pregnanol-3($\beta$)one-20 thus obtained oxidized with chromic acid in acetic acid at room temperature to give 5,6,17,21-tetrabromo-pregnandione-3-20 and the latter treated with 2 moles of potassium iodide in boiling alcohol to obtain 17,21-dibromo-$\Delta^4$-pregnenedione-3,20 of formula

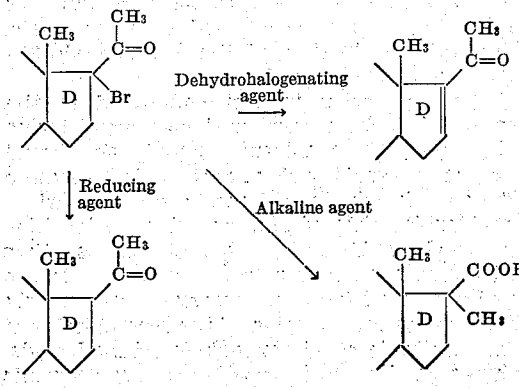



Again the presence of nuclear ketone groups in the 20-keto-pregnane compound being halogenated may result in nuclear halogenation at methylene groups adjacent to the nuclear ketone grouping. Thus, pregnanedione-3,20 on chlorination yields a mixture of chloro-pregnanediones containing from one to four chlorine atoms at positions 2, 4, 17 and 21; the order of substitution being in the main 4, 17, 21 and 2 in the "regular" and 2, 17, 21 and 4 in the "allo" series. The same order of halogenation occurs in both series when trihalogenating or dihalogenating. When dihalogenating, for example, the main reaction in the regular series appears to go as illustrated by the following:



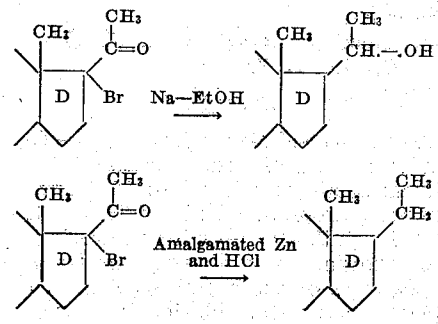

While the presence in rings A, B or C of a carbon-to-carbon double bond or a ketone grouping may result in the halogen attacking at these groupings, practically all other groupings remain unaffected by the halogen. Halogen atom or ester groupings in rings A, B or C remain unaffected during the halogenation. If the halogenation is conducted in a liquid lower organic acid, such as acetic acid, hydroxyl groups in the nucleus may be esterified by the catalytic action of the hydrohalic acid formed as a by-product during the halogenation. This is illustrated in Example 7A.

The reactions of the 17-bromo-20-keto-pregnane compounds are summarized in the diagram below.



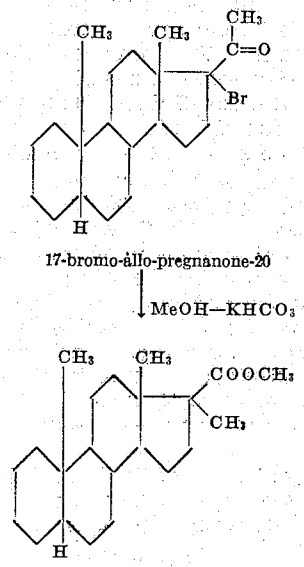

As the above diagram indicates the 17-bromo-20-keto pregnane compounds are readily reduced to 20-keto-pregnane compounds by numer-

ous agents including catalytic hydrogenation in the presence of a palladium catalyst and preferably in the presence of a tertiary base such as pyridine, triethylamine or dimethylaniline, or the combination of a metal, such as iron, zinc, tin, magnesium or aluminum and a substance reactive therewith to form nascent hydrogen, such as organic acids like acetic acid, lactic acid, etc. If a strong reducing agent, capable of reducing a ketone group, is employed, the intermediately formed 20-keto-pregnane compound will be further reduced. This is illustrated in the following diagram.




The action of dehydrohalogenating agents on 17-bromo-20-keto-pregnane compounds leads to $\Delta^{16}$-unsaturated 20-keto-pregnane compounds. Dehydrohalogenating agents suitable for this purpose include the combination of an organic acid and an inorganic salt of an organic acid, also a tertiary base. It has been found that potassium acetate and acetic acid, sodium acetate in acetic acid and also pyridine are particularly satisfactory dehydrohalogenating agents, but of course other substances may be used such as sodium benzoate in valeric acid, dimethylaniline, quinoline, triethanolamine, etc.

The action of alkaline agents on a 17-bromo-20-keto-pregnane compound leads to molecular rearrangement with the formation of a 17-methyl-etio-cholanic acid or a derivative of the carboxyl group thereof. For example, if 17-bromo-allo-pregnanone-20 is refluxed with methanolic potassium bicarbonate, there is obtained the methyl ester of 17-methyl-etio-allo-cholanic acid, as illustrated below.

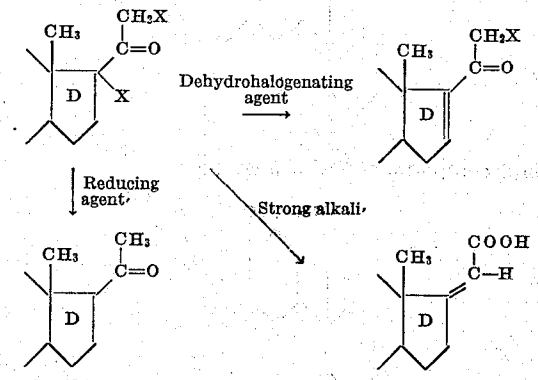



Methyl 17-methyl-etio-allo-cholanate

The new esters of the type of methyl 17-methyl-etio-allo-cholanate are very resistant to hydrolysis which may account in part for the surprising result that an ester is obtained from a reaction which would ordinarily be expected to yield a hydrolyzed product. The reaction mechanism is obscure, but it appears that the nature of the product is determined by the nature of the solvent employed. For example, if ethanolic sodium bicarbonate, instead of methanolic bicarbonate, is reacted with 17-bromo-allo-pregnanol-20, the product is ethyl 17-methyl-etio-allo-cholanate.

As has already been indicated, the 17-bromo-20-keto-pregnane compounds may be further halogenated, thereby forming 17,21-dihalo-20-keto-pregnane compounds. By using, for the second step of halogenation, a halogen different from that already present at C–17 a mixed 17,21-dihalo-20-keto-pregnane compound can be obtained. Thus 17-chloro-allo-pregnanone-20 may be brominated at 35° C. with formation of 17-chloro-21-bromo-allo-pregnanone-20.

The reactions of the 17,21-dihalo-20-keto-pregnane compounds are summarized in the following diagram:



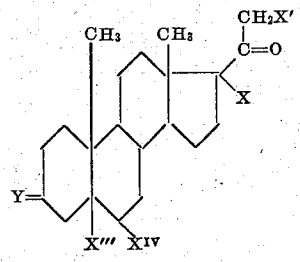

As the above diagram shows, the reactions of the 17,21-dihalo-20-keto-pregnane compounds are somewhat analogous to the reactions of the 17-halo-20-keto-pregnane compounds. Thus both classes of compounds are reduced with formation of 20-keto-pregnane compounds, both classes of compounds can be dehydrohalogenated with formation of unsaturated steroids and both classes of compounds undergo molecular rearrangement when treated with alkaline agents. The remarks that have been made as to the type of reagents useful in reactions with 17-halo-pregnane compounds apply also in the case of 17,21-dihalo-20-keto-pregnane compounds. Thus the reduction of 17,21-dihalo-20-keto-pregnane compounds to 20-keto-pregnane compounds can be effected by reagents such as zinc and acetic acid, iron and acetic acid, or catalytic hydrogenation in the presence of palladium and pyridine, or more generally by (*a*) the combination of a metal and a substance reactive therewith to form nascent hydrogen and (*b*) catalytic hydrogenation in the presence of palladium and a tertiary amine. It has also been found that the combination of formic acid and a salt thereof is a satisfactory reducing agent for this reaction.

The dehydrohalogenation of 17,21-dihalo-20-keto-pregnane compounds to 21-halo-$\Delta^{16}$-unsaturated 20-keto-pregnane compounds can be affected by reagents such as potassium acetate and acetic acid.

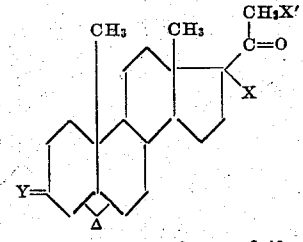
The treatment of a 17,21-dihalo-20-keto-pregnane compound with strong alkali leads to the formation of a $\Delta^{17}$-21-pregnenoic acid or a deriva-

tive at the carboxyl group thereof. The reaction is best conducted in an alcoholic solution using a large excess of strong alkali. Under these conditions there is formed, along with free $\Delta^{17}$-21-pregnenoic acid, a quantity of the ester thereof with the alcohol used as a solvent. For example, methanolic potassium hydroxide and 17,21-dibromo-allo-pregnanone-20 yield $\Delta^{17}$-21-allo-pregnenoic acid together with some methyl $\Delta^{17}$-21-allo-pregnenoate. If the reaction is conducted in ethanol or propanol there is obtained, instead of the methyl ester, the ethyl ester or the propyl ester, respectively. Other strong bases may be used instead of potassium hydroxide, such as bases including sodium hydroxide, sodium ethylate, potassium methylate, etc.

It will be appreciated that this invention comprehends several new classes of steroids, of which an important group consists of compounds of the formula

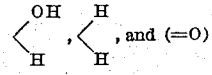


and compounds of the formula



where X and X′ are members of the class consisting of chlorine and bromine, X‴ and $X^{IV}$ are members of the class consisting of chlorine, bromine and hydrogen, $X^{IV}$ being hydrogen when X‴ is hydrogen and X‴ being the same as $X^{IV}$ when the latter is one of the class chlorine and bromine, Y is a member of the class consisting of

groups hydrolyzable to



and Δ represents a carbon-to-carbon double bond included between $C_5$ and one of $C_4$ and $C_6$.

This invention may be further illustrated by the following examples.

*Example 1*

A. *17-bromo-allo-pregnanone-20.*—To a solution of 10 g. of allo-pregnanone-20 in 200 cc. of glacial acetic acid is added 10 drops of concentrated hydrobromic acid and 33.2 cc. of a 1 M. (1 molar) solution of bromine in acetic acid. After standing fifteen minutes the solution is poured into water, extracted with ether and the ethereal extract washed free of acetic acid with water and dilute sodium carbonate solution. Evaporation of the ether gives a residue which is crystallized from ether-methanol and acetone to give crystals, M. P. 127–9 C., of 17-bromo-allo-pregnanone-20. This product depresses the melting point of allo-pregnanone-20, M. P. 132°, by twenty degrees.

Anal. calcd. for $C_{21}H_{33}OBr$: C, 66.2; H, 8.7. Found: C, 65.8; H, 8.8.

B. *17,21-dibromo-allo-pregnanone-20.*—To 500 mg. of 17-bromo-allo-pregnanone-20 in 35 cc. of glacial acetic acid is added at 35° C. 2 drops of 45% aqueous hydrobromic acid and 1.3 cc. of 1.0 M. bromine in acetic acid. After standing for one hour the solution is diluted with water, filtered, and the solid washed with water. Crystallization from acetone yields a product melting at 128–130° C. This is 17,21-dibromo-allo-pregnanone-20.

Anal. calcd. for $C_{21}H_{32}OBr_2$: C, 55.0; H, 6.6. Found: C, 54.8; H, 7.0.

*Example 2*

*17,21-dibromo-allo-pregnanone-20.*—To a solution of 5 g. of allo-pregnanone-20 in 100 cc. of glacial acetic acid is added 10 drops of concentrated hydrobromic acid and 33.2 cc. (2 mols.) of a 1 M. solution of bromine in acetic acid, the rate of addition being governed by the speed of disappearance of the bromine color. To ensure complete reaction the solution is warmed to 40° C. during the addition of the second mol of bromine. The solution is allowed to stand for thirty minutes, then poured into 500 cc. of ice-water and filtered. The rather gummy precipitate is taken up in ether, washed with water and saturated sodium bicarbonate solution and the ether evaporated. The residue is crystallized from acetone to give 17,21-dibromo-allo-pregnanone-20, M. P. 128–30° C. This gives a depression when mixed with a sample of either 17-bromo-allo-pregnanone-20, M. P. 127° C. or allo-pregnanone-20, M. P. 132° C.

*Example 3*

A. *17-bromo-allo-pregnanol-3(β)-one-20.*—To a solution of 17 g. of allo-pregnanol-3(β)-one-20 in 1 liter of acetic acid is added at room temperature, dropwise, 54 cc. of a 1 M. solution of bromine in acetic acid. The solution is allowed to stand ten minutes, and then 1 liter of water is added. The gummy precipitate is collected, taken up in ether, the ethereal layer washed well with water, and then evaporated. The residue is crystallized from aqueous methanol and from ether-pentane. The product, 17-bromo-allo-pregnanol-3(β)-one-20, has M. P. 93–96° C.

Anal. calcd. for $C_{21}H_{33}O_2Br$: C, 63.5; H, 8.4. Found: C, 63.6; H, 8.1.

B. *17,21 - dibromo-allo-pregnanol-3(β)-one-20 acetate.*—To a solution of 18 g. of 17-bromo-allo-pregnanol-3(β)-one-20 in 1 liter of acetic acid is added, at 40° C. one equivalent of a 1 M. solution of bromine in acetic acid. After the bromine has reacted, the solution is diluted with water and the precipitate is taken up in ether. The ethereal layer is washed with water, dilute sodium carbonate solution, and finally with water. The ether is removed and the residue is crystallized from methanol. The purified 17,21-dibromo-allo-pregnanol-3(β)-one-20 acetate has M. P. 174° C.

The esterification of the 3—OH during the reaction is probably due to the catalytic effect of the hydrogen bromide present.

*Example 4*

A. *17-bromo-pregnanol-3(β)-one-20 acetate.*—A solution of 5 g. of pregnanol-3(β)-one-20 acetate and two drops of 48% hydrobromic acid in

150 cc. of glacial acetic acid is warmed to 30° C. Then 14.0 cc. of a 1 M. solution of bromine in acetic acid is added dropwise. After standing for fifteen minutes, the mixture is poured into water and the precipitated solid collected and extracted with ether. The ethereal extract is washed with water, 5% sodium bicarbonate solution and again with water. Then the ether is removed on a steam bath and the residue crystallized from methanol to give compact white crystals of 17-bromo-pregnanol-3(β)-one-20 acetate of M. P. 152–154° C.

Anal. calcd. for $C_{23}H_{35}O_3Br$: C, 62.9; H, 8.0. Found: C, 63.0; H, 7.8.

*Example 5*

A. *17-bromo-pregnanol-3(β)-one-20.*—To a solution of 1.0 g. of pregnanol-3(β)-one-20 in 50 cc. of glacial acetic acid at 25° C. is added 2 drops at 48% hydrobromic acid. Then 3.13 cc. of a 1 M. solution of bromine in acetic acid is added slowly. After the bromine is all absorbed, the mixture is poured into water and the precipitated solid collected and washed with water. The product is crystallized from ether to give compact white crystals of 17-bromo-pregnanol-3(β)-one-20 of M. P. 169–171° C.

Anal. calcd. for $C_{21}H_{33}O_2Br$: C, 63.5; H, 8.4. Found: C, 63.1; H, 8.3.

*Example 6*

A. *17,21-dibromo-pregnanol-3(β)-one-20 acetate.*—A solution of 5 g. of pregnanol-3(β)-one-20 acetate in 150 cc. of glacial acetic acid containing 2 drops of 48% hydrobromic acid is warmed to 40° C. and then 29 cc. of 1 M. bromine in acetic acid is added dropwise. After the solution has stood for fifteen minutes it is poured into water and the precipitated solid collected and washed with water. The solid is recrystallized from acetone to give white crystals of 17,21-dibromo-pregnanol-3(β)-one-20 acetate of M. P. 190–191° C.

Anal. calcd. for $C_{23}H_{34}O_3Br_2$: C, 53.3; H, 6.6. Found: C, 52.9; H, 6.7.

*Example 7*

A. *17,21-dibromo-pregnanol-3(β)-one-20.*—To a solution of 10 g. of pregnanol-3(β)-one-20 in 300 cc. of glacial acetic acid at 40° C. is added several drops of 48% hydrobromic acid. Then 62.6 cc. of 1 M. bromine in acetic acid is added dropwise. After the addition of bromine is completed, the solution is poured into water and the precipitated solid collected and washed with water. The solid is crystallized from ether to give thick white needles of 17,21-dibromo-pregnanol-3(β)-one-20 of M. P. 190–192° C.

*Example 8*

*17-bromo-allo-pregnanol-3(β)-one-20 acetate.*—To a solution of 11 g. of allo-pregnanol-3(β)-one-20 acetate in 500 cc. of acetic acid is added dropwise at room temperature 31 cc. of 1 M. bromine in acetic acid. After the solution has stood for one hour, ice and cold water are added and the mixture is extracted with ether. The ethereal layer is separated and washed with dilute sodium carbonate solution and water. Then the ether is evaporated and the residue crystallized from methanol to give 17-bromo-allo-pregnanol-3(β)-one-20 acetate of M. P. 155° C.

*Example 9*

*17-chloro-allo-pregnanol-3(β)-one-20 acetate.*—A 1% solution of chlorine in chloroform is standardized by titration of the available chlorine, for example with potassium iodide and starch.

To a solution of 1 g. of allo-pregnanol-3(β)-one-20 acetate in 30 cc. of acetic acid at 30° C. is added 10 cc. of an accurately standardized 1% solution of chlorine in chloroform. After the mixture has stood for an hour it is diluted with water and extracted with ether. The ethereal extract is washed with sodium bicarbonate solution and with water and then the extract is evaporated on a steam bath. The residue is 17-chloro-allo-pregnanol-3(β)-one-20 acetate. It may be purified by crystallization from dilute acetone.

*Example 10*

A. *5,6,17,21-tetrabromo-pregnanol-3(β)-one-20 acetate.*—To a solution of 10 g. of $\Delta^5$-pregnenol-3(β)-one-20 acetate in 200 cc. of acetic acid is added 28.5 cc. of a 1 M. solution of bromine in acetic acid. Then a few drops of 48% hydrobromic acid are added, followed by an additional 57 cc. of 1 M. bromine in acetic acid. The solution is warmed to 40° C. to insure complete reaction and then the mixture is allowed to stand at room temperature. After several hours the solid which has deposited is collected and washed with ether. This is 5,6,17,21-tetrabromo-pregnanol-3(β)-one-20 acetate of M. P. 172° C. dec.

Anal. calcd. for $C_{23}H_{32}O_3Br$: C, 40.8; H, 4.8. Found: C, 40.6; H, 4.8.

Bromination of $\Delta^5$-pregnenol-3(β)-one-20 by the same procedure gives the same product, 5,6,17,21-tetrabromo-pregnanol-3(β)-one-20 acetate.

B. *17,21-dibromo-$\Delta^5$-pregnenol-3(β)-one-20 acetate.*—A solution of 4.36 g. of sodium iodide in 100 cc. of alcohol is added to a boiling solution of 10 g. of 5,6,17,21-tetrabromo-pregnanol-3(β)-one-20 acetate in 1500 cc. of ethanol and the mixture boiled for an hour. Then water is added and the mixture is extracted with ether. The ethereal extract is washed with dilute sodium bicarbonate solution and with water and then the ether is removed on the steam bath. The residue is 17,21-dibromo-$\Delta^5$-pregnenol-3(β)-one-20 acetate. It may be purified by crystallization from dilute acetone. However, this is unnecessary if the substance is to be used in the next step.

*Example 11*

A. *5,6,17,21-tetrabromo-pregnanol-3(β)-one-20 propionate.*—To a solution of 0.60 g. of $\Delta^5$-pregnenol-3(β)-one-20 in 10 cc. of propionic acid is added 5.37 cc. of a 1 M. solution of bromine in chloroform. After all the bromine is absorbed the mixture is diluted with water and extracted with ether. The ethereal extract is washed with water and the ether evaporated on a steam bath. The crystalline residue may be purified by leaching it with ether. Thus, there is obtained 5,6,17,21-tetrabromo-pregnanol-3(β)-one-20 propionate, M. P. 175° C. dec.

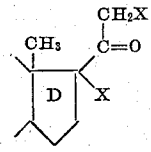
The same product is obtained when $\Delta^5$-pregnenol-3(β)-one-20 propionate is treated with bromine in the manner described above.

While this invention has been described and illustrated with especial reference to certain forms of the invention, and these forms have been explained in terms of a particular theory, it is to be understood that this invention is not limited to these specific forms, nor is its operability in any way affected by the ultimate cor-

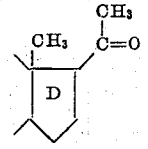
rectness of the particular theories herein employed.

What we claim as our invention is:

1. Process for the preparation of a halosteroid having at ring D the structure

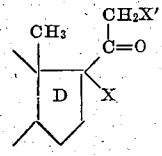


where X is a member of the class consisting of chlorine and bromine which comprises reacting a steroid having at ring D the structure

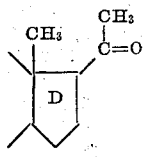


with a member of the class consisting of chlorine and bromine.

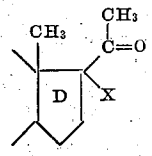
2. Process for the preparation of a halosteroid having at ring D the structure



where X and X' are members of the class consisting of chlorine and bromine which comprises reacting, under relatively mild conditions, a steroid having at ring D the structure

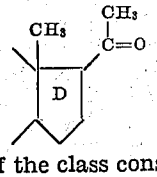


with a member of the class consisting of chlorine and bromine, and further halogenating the steroid having at ring D the structure

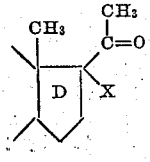


thus produced by reacting it above 30° C. with a member of the class consisting of chlorine and bromine.

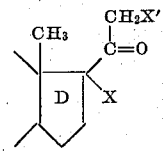
3. In a process according to claim 2, the step which comprises reacting, under relatively mild conditions, a steroid having at ring D the structure



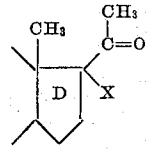
with a member of the class consisting of chlorine and bromine thereby producing a steroid having at ring D the structure



4. Process for the preparation of a halosteroid having at ring D the structure

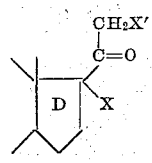


where X and X' are members of the class consisting of chlorine and bromine which comprises halogenating a steroid having at ring D the structure



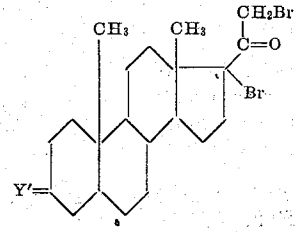
where X is a member of the class consisting of chlorine and bromine by reacting said steroid above 30° C. with a member of the class consisting of chlorine and bromine.

5. A halosteroid having in ring D the formula



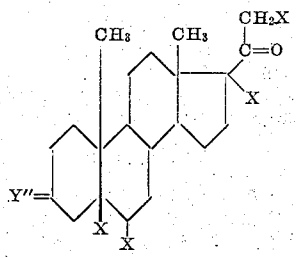
where X and X' are members of the class consisting of chlorine and bromine.

6. A halosteroid of the formula



where Y' represents

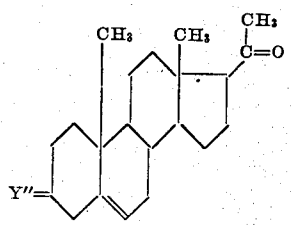
7. Process for the preparation of a halosteroid of the formula



where the X groups are members of the class consisting of chlorine and bromine and Y'' is a member of the class consisting of

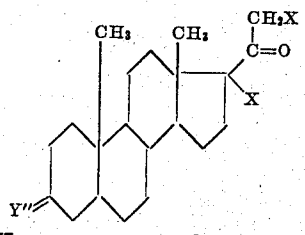
and groups hydrolyzable to

which comprises reacting a steroid of the formula



with a member of the class consisting of chlorine and bromine the quantity of said halogenating agent being at least six gram-atoms per gram-mole of said steroid.

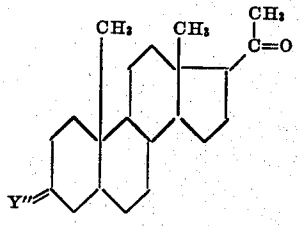
8. Process for the preparation of a halosteroid of the formula



where the X groups are members of the class consisting of chlorine and bromine and Y'' is a member of the class consisting of

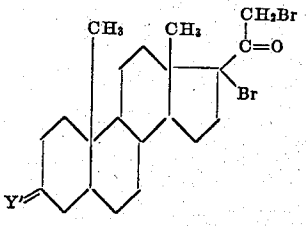
and groups hydrolyzable to

which comprises reacting a steroid of the formula



with a member of the class consisting of chlorine and bromine the quantity of said halogenating agent being at least four gram-atoms per gram-mole of said steroid.

9. A halosteroid of the formula



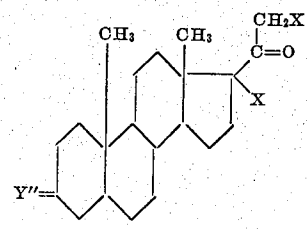
where Y' represents

10. A lower fatty acid ester of a 17,21-dibromo-pregnanol-3-one-20.

11. 17,21-dibromo-pregnanol-3(β)-one-20 acetate melting at approximately 190–191° C.

12. 17,21-dibromo-pregnanol-3(β)-one-20 melting at approximately 190–192° C.

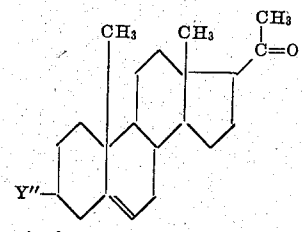
13. Process for the preparation of a halosteroid of the formula



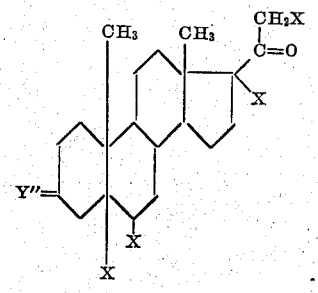
where X is a member of the class consisting of chlorine and bromine and Y'' is a member of the class consisting of

and groups hydrolyzable to

which comprises reacting a steroid of the formula



with at least six gram-atoms per gram-mole of said steroid, of a member of the class consisting of chlorine and bromine, and subjecting the tetra-halosteroid of formula



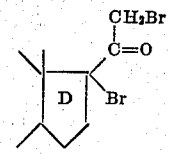
thus formed to partial dehalogenation by treating it with a soluble iodide.

14. Process for preparing a lower fatty acid ester of a 17,21-dibromo-pregnanol-3-one-20 which comprises reacting a lower fatty acid ester of pregnanol-3-one-20 with at least four gram-atoms of bromine per gram-mole of ketone.

15. Process for preparing 17,21-dibromo-pregnanol-(β)-one-20 acetate which comprises reacting pregnanol-3(β)-one-20 acetate in acetic acid at 30–100° C. with at least four gram-atoms of bromine per gram-mole of ketone.

16. Process for preparing 17,21-dibromo-pregnanol-3(β)-one-20 which comprises reacting pregnanol-3(β)-one-20 with at least four gram-atoms of bromine per gram-mole of ketone.

17. A halosteroid having in ring D the formula



18. 17,21-dibromo-$\Delta^4$-pregnenedione-3,20.

RUSSELL EARL MARKER.
HARRY M. CROOKS, JR.