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UNITED STATES PATENT OFFICE

2,461,912

PROCESS FOR THE DEGRADATION OF THE SIDE-CHAIN OF A STEROID CONTAINING A NUCLEAR α,β-UNSATURATED KETO GROUP

Karl Miescher, Riehen, Hugo Frey, Olten, and Charles Meystre and Albert Wettstein, Basel, Switzerland, assignors to Ciba Pharmaceutical Products, Inc., Summit, N. J.

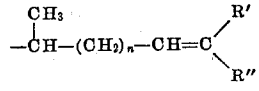
No Drawing. Application April 28, 1947, Serial No. 744,534. In Switzerland August 18, 1942

6 Claims. (Cl. 260—397.3)

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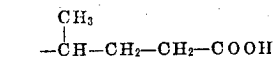
This application is a continuation-in-part of our application Serial No. 687,694, filed August 1, 1946, which is a continuation-in-part of our application Serial No. 657,896, filed March 28, 1946, which is a continuation-in-part of our application Serial No. 497,556, filed August 5, 1943.

In application Serial No. 497,556 and in continuation-in-part Serial No. 581,963, filed March 9, 1945 (now abandoned), we disclosed processes for the degradation of the side-chain of steroids which makes possible the removal of at least three of the carbon atoms originally contained in the side-chain. These already disclosed new processes comprise causing ring-saturated or ring-unsaturated steroids which contain in 17-position a substituent

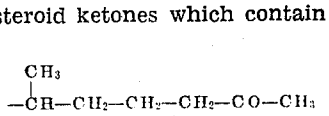


wherein R′ and R″ represent hydrogen, an aliphatic, aromatic or hydroaromatic radical, and n means the number 1 or 2, if necesary with temporary protection of nuclear double bonds and sensitive substituents, to react with carboxylic acid imides, amides or arylamides which are substituted by halogen at the nitrogen atom, subsequently treating the products obtained with agents capable of eliminating hydrogen halide, (any ammonium compounds, acyloxy derivatives or ethers intermediately produced being subjected to heat) and finally splitting up the newly formed conjugated double bond by means of oxidizing agents, if necessary with temporary protection of nuclear double bonds and sensitive substituents. In one form of the process a hydroxyl group is converted into a keto-group before the oxidative splitting of the conjugated system.

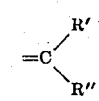
The starting materials for our already disclosed new processes can be prepared, for example, from functional derivatives such as esters, halides or anhydrides of steroid carboxylic acids, which contain in the 17-position the radical



or from steroid ketones which contain the side-chain



by known methods. Examples of such acids are, in particular, cholic acid, desoxycholic acid, chenodesoxycholic acid, hyodesoxycholic acid, lithocholic acid, cholanic acid, allocholanic acid, ursocholanic acid, Δ^5-3-hydroxy-cholenic acid, Δ^7-3,12-dihydroxy-cholanic acid and apocholic acid; examples of ketones are norcholestane-3-ol-25-one and Δ^5-nor-cholestene-3-ol-25-one. In addition to the acids and ketones mentioned, there may be used starting materials derived from corresponding derivatives, substitution or conversion products containing any substituents, particularly keto-groups; also those derived from the next higher homologues of the acids and the next lower homologues of the ketones mentioned. Such carboxylic acid derivatives or ketones can be caused to react with organic compounds of magnesium or other metals, e. g. methyl, ethyl or phenyl magnesium halides, and water can be eliminated directly or indirectly from the tertiary carbinols obtained. In addition to the ethylene compounds produced in the manner described, compounds of the type of dehydro-norcholene (see, Wieland and co-workers, Zeitschrift für physiologische Chemie, 150, page 273 [1925]; ibidem, 186, page 229 [1930]) are suitable for use as starting materials. In these compounds the group



is represented by the carbon atom 12 and the residual cyclopentanopolyhydrophenanthrene structure.

A number of methods for the degradation of the side-chain of steroids are already known. For instance, the gradual degradation of bile acids by Wieland's or Curtius' method is widely used, which methods have to be repeated several times, as only one carbon atom is removed at a time. These processes are therefore very tedious and expensive and, in addition, only give very moderate yields. The radical oxidation of sterols with chromic acid is simpler. But in this case too, only a little part of the parent compound is converted into products with a largely or completely degraded side-chain. To a considerable extent the side-chain is only insufficiently degraded e. g. down to the stage of nor-cholestane-25-one or of cholanic acid, or the nucleus is split up under the vigorous conditions of the reaction. If the partly degraded products of the reaction are again strongly oxidized, the total yield decreases quite considerably, calculated on the amount of the twice oxidized parent substance. This is all the more pronounced as compounds of the cholanic acid series give worse results on vigorous oxidation, than the sterols. Finally

many steroids, substituted in the nucleus in a special way, only occur in nature in the form of the cholanic acids and not as the corresponding sterols. For these reasons, a process which allows compounds of the cholanic acid or the norcholestane-25-one series to be degraded to a considerable degree with a good yield and in a clear and easy manner, represents a considerable advance.

In the first stage of our already disclosed new processes, derivatives of imides of dicarboxylic acids which are substituted by halogen (e. g. bromine or chlorine) at the nitrogen atom, are caused to act on the parent materials; as examples of such derivatives may be given N-halogen succinimides, phthalimides, parabanic acids, cyanuric acids, hydantoins or barbituric acids. In their stead corresponding derivatives of primary or secondary carboxylic acid amides, such as acetamide, propionamide or diacetamide, or of carboxylic acid arylamides, e. g. acetanilides and benzanilides halogenated or nitrated in the nucleus, may also be used. To carry out halogenation of the methylene group, which is present in the substituent mentioned in the α-position to the double bond, it is best to work in an inert solvent or diluent such as carbon tetrachloride, chloroform, benzene, cyclohexane, methyl-cyclohexane, ethyl ether or dioxane.

Double bonds which may be present in the cyclopentanopolyhydrophenanthrene nucleus can be temporarily protected during halogenation in the usual way by saturation with halogen or hydrogen halide. The latter has the special advantage that the double bonds are regenerated in the next stage by means of basic reagents. Finally, substituents which are sensitive to halogenating agents may be advantageously protected temporarily, particularly free hydroxyl groups, for example, by esterification or etherification. The esters with aromatic acids such as benzoic acid are, in contrast to the free hydroxyl compounds, very stable to the above halogenating agents; the esters with aliphatic acids are also generally attacked more slowly than the active methylene groups. Free keto groups also react considerably more slowly and hardly need to be protected. If necessary they can be converted into acetals, in particular of glycols. Free carboxyl groups do not react in general and therefore generally do not need special protection.

The halogenated products are subjected, either in the crude form or after purification, to a treatment eliminating hydrogen halide, e. g. they are treated with agents capable of eliminating hydrogen halide, for instance with basic agents, such as amines like collidine, quinoline, dimethylaniline, pyridine or cyclohexylamine, with alkaline or alkaline earth hydroxides or carbonates; instead of them also carboxylic acid salts such as the alkali or silver salts of fatty acids or even alcohols or phenols may be used. According to the reagents used and the conditions of the reaction, the reactive halogen is directly eliminated in the form of hydrogen halide and/or there are formed ammonium halides by the action of tertiary amines (e. g. pyridinium halides which, owing to their insolubility in ether, are easy to separate), acyloxy derivatives by the action of carboxylic acid salts, or ethers by the action of alcohols or phenols. Ammonium halides, ammonium bases obtained from them, acyloxy derivatives and ethers are subsequently advantageously decomposed by heat, preferably in a vacuum or in an inert gas, so that an elimination of hydrogen halide is produced in stages. Instead of the agents capable of eliminating hydrogen halide, there can be used appropriate measures, such as heating, evacuating, or the said agents and measures can also be combined. Reaction products with conjugated double bonds containing acyloxy groups which have been obtained can subsequently be completely or partially saponified.

The conjugated double bond newly formed in the reaction products is then split up by direct or indirect oxidation in known manner. We mention, for example, oxidation by means of a compound of hexavalent chromium (such as chromic acid), permanganate, ozonisation and splitting of the ozonides, the action of peroxides such as perbenzoic acid, monoperphthalic acid or hydrogen peroxide (preferably in the presence of osmium tetra-oxide), and splitting (by means of, for example, chromic acid, lead tetra-acylates or periodic acid) of the glycols formed by hydrolysis of the oxide-ring or by direct addition of two hydroxyl groups to each of the double bonds.

During the oxidation, the double bonds contained in the cyclopentanopolyhydrophenanthrene nucleus may also be temporarily protected, for example, by addition and subsequent elimination of halogen or hydrogen halide, provided such protection is not made unnecessary by the special properties of the unsaturated system, such as, for example, a double bond with a keto group in the α-position. In addition, other sensitive substituents such as hydroxyl groups may be protected in known manner, e. g. by esterification or etherification and after oxidation again liberated, if desired, partly or completely by hydrolysis. If, however, conversion of the nuclear hydroxyl groups to keto groups is desired, it can be carried out in known way, before, during or after oxidative cleavage of the conjugated double bond by the action of, in particular, oxidizing or dehydrogenating agents. Also chromic acid, permanganates, etc. are suitable oxidizing agents for this purpose; as dehydrogenating agents may be used, in particular, metal alcoholates or phenolates and carbonyl compounds (method of exchanging oxidation stages), or for example powdered metal by heating in a vacuum.

The products obtained by the new simple process, ketones, carboxylic acids or aldehydes can be separated as usual and purified, for example, by recrystallization, chromatography, sublimation, reaction with keto reagents (particularly with those which give water-soluble condensation products), or by extraction with solutions of strong acids or their salts, or with basic reagents. They are themselves used for therapeutic purposes or may serve as intermediate products in the manufacture of medicaments.

In the halogenation step of the above described new processes it is sometimes necessary to use a large excess of one of the reaction components in order to obtain a moderately satisfactory result. The halogenated intermediate products split off hydrogen halide very easily, which latter reacts with the excess of halogenating agent to liberate halogen which in turn gives rise to side reactions.

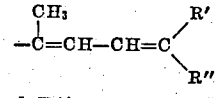
The application Serial No. 657,896 and the continuation-in-part Serial No. 687,694 are based on the unexpected observation that, contrary to earlier statements, the introduction of halogen in α-position to the double bond by the action of a carboxylic acid imide, amide or aryl-amide

halogenated at the nitrogen is considerably facilitated by exposure to light. This improvement in the process leads to a series of advantages. The speed of reaction must be mentioned primarily. By virtue thereof side reactions are practically precluded, and this makes it possible for the first time to isolate the primarily formed halogenation products. A further advantage is that reactants can be used in approximately stoichiometric quantities. Finally, the favourable influence of the illumination on the yield must be especially emphasized.

In other respects the process of the application Serial No. 657,896 and continuation-in-part Serial No. 687,694 is carried out in the manner described in our aforesaid application Serial No. 497,556 and continuation-in-part Serial 581,963 with regard to the reaction components to be used as starting materials, the solvents, etc. It is only necessary to emphasize the ease with which hydrogen halide can be eliminated from the halogenation products, whose isolation in pure form now became possible by virtue of the process. The elimination of hydrogen halide could be brought about by simple heating, so that after the treatment with the halogenating agent it is only necessary to continue the boiling in order to obtain the diene. The improved process is of special advantage for the production of progesterone by starting from $\Delta^{5:23}$-3-hydroxy-24:24-diphenyl-choladiene by way of the corresponding triene. Either the hydroxy group in the triene is dehydrogenated to the keto-group and then the conjugated system is subjected to oxidative splitting, or the acylated or free triene is first oxidized to the methyl ketone stage and the resulting compound is converted in known manner into progesterone. The nuclear double bond may be protected, especially in the first step of the process, for example, by the addition of hydrogen halide or halogen. $\Delta^{5:23}$-3-hydroxy-24:24-diphenyl-choladiene serving as starting material can be easily obtained from Δ^{5}-3-hydroxy-cholenic acid. The latter acid is formed as a hitherto valueless by-product in the side chain degradation of cholesterol to dehydroandrosterone. By this process the yield of progesterone, as compared with that obtained by the process of the aforesaid specifications, is increased many times.

For the exposure to light there may be used various sources of illumination which may or may not contain ultra-violet constituents, for example, the light from incandescent lamps, quartz lamps or arc lamps, or strong natural light such as the direct rays of the sun.

The invention was concerned with a process for the preparation of steroids which in 3-positions have a free hydroxyl group and in 5-position a halogen atom, such as chlorine or bromine, and which carry in 17-position the acetyl group or a substituent of the formula



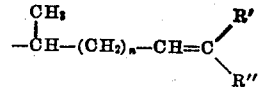
wherein R′ and R″ represent hydrogen atoms, aliphatic, aromatic, or hydroaromatic radicals.

The invention was further concerned with a process for the preparation of progesterone wherein corresponding compounds of the constitution mentioned are used as starting materials.

The surprising discovery was made that 3-acyloxy-steroids, which in 5-position have a halogen atom and in 17-position one of the above mentioned substituents, can be converted into

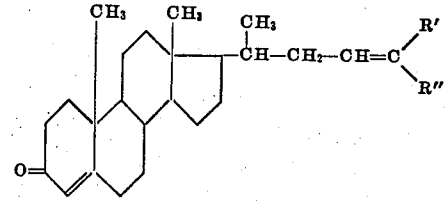
5-halogen steroids carrying a free hydroxyl group in 3-position by treatment with acid hydrolyzing agents. In the compounds so obtained the free oxy group in 3-position can be converted into a keto group and the conjugated double-linkages in the side-chain may simultaneously or subsequently be split up. From the so formed 3-keto-5-halogen compounds hydrogen halide may be eliminated while a double linkage is formed. There may be used as acid hydrolyzing agents inorganic acids such as, for instance, a hydrohalic acid or sulfuric acid, advantageously in the presence of water and an organic solvent, like ethyl alcohol, acetone, dioxane, benzene, or mixtures thereof. Concerning the remaining agents and conditions of the reaction, the process may be carried out in a manner analogous to that described above. The defined process was of special advantage in making progesterone.

The new invention is concerned with a process for the degradation of steroids, which contain an α,β-unsaturated keto group in the nucleus and in 17-position a substituent



wherein R′ and R″ represent hydrogen, an aliphatic, aromatic or hydroaromatic radical, and n means the number 1 or 2.

The new invention is also concerned with a process for the preparation of progesterone, wherein a compound of the formula



R′ and R″ having the above meaning, is used as starting material.

We now made the discovery that the halogenation of such starting materials under exposure to light proceeds much more rapidly in the side chain than in the allyl-position of the nuclear double bond, so that one need not protect the latter. That gives the possibility to prepare degradation products, containing an α,β-unsaturated keto group in the steroid nucleus, and especially progesterone, in a much simpler manner by halogenating the said starting materials, splitting off hydrogen halide and splitting up the newly formed conjugated double bond in the reaction products. Concerning the agents and conditions of those reactions the new process may be carried out in a manner analogous to that described above.

The following examples illustrate the whole invention but are not to be regarded as limiting it in any way, the parts mentioned being by weight:

Example 1

10 parts of Δ^{23}-3-acetoxy-5-chloro-24:24-diphenyl-cholene melting at 178–181° C. (obtained, for example, from Δ^{5}-3-hydroxycholenic acid methyl ester by reaction with a phenyl magnesium halide followed by partial acetylation of the resulting carbinol with acetic anhydride in the cold, splitting off the tertiary hydroxyl group by boiling in glacial acetic acid and saturating the double bond in the 5-position with hydrogen chloride) and 3.1 parts of bromosuccinimide are heated at

the boil in 150 parts of carbon tetrachloride while exposed to the light from a powerful incandescent lamp. In a few minutes the reaction is finished. The solution is then cooled with ice-water, and the resulting succinimide is separated by filtering with suction.

In order to eliminate hydrogen bromide and hydrogen chloride the clear filtrate is mixed with dimethylaniline, the carbon tetrachloride is removed by distillation, and the concentrated solution is heated at the boil for a short time. The product is then taken up in ether, the dimethylaniline is removed by agitation with hydrochloric acid and water, and the ethereal solution is dried and evaporated.

For the purpose of hydrolysis the residue, which contains crude $\Delta^{5,20,23}$-3-acetoxy-24:24-diphenyl-cholatriene, is boiled in a reflux apparatus in 100 parts of ethanol with 3 parts of potassium hydroxide for 45 minutes, the solution is evaporated under reduced pressure, and the residue after dissolution in ether is washed with water. After drying and evaporating, crude $\Delta^{5,20,23}$-3-hydroxy-24:24-diphenyl-cholatriene is obtained.

To effect oxidation in the 3-position the crude triene is boiled with a solution of 90 parts of cyclohexanone in toluene, and into the slowly distilling solution is introduced dropwise a solution of 1.7 parts of aluminium isopropylate in toluene. The cooled solution is then mixed with an aqueous concentrated solution of Seignette's salt, and subjected to steam distillation. The cooled distillation residue is filtered with suction, washed with water and dried. The crude $\Delta^{4,20,23}$-3-keto-24:24-diphenyl-cholatriene so obtained is further worked up without purification.

It is taken up, for example, in a mixture of 450 parts of chloroform, 270 parts of glacial acetic acid and a little water, and slowly mixed, while stirring and cooling with ice, with a solution of about 8 parts of chromium trioxide in 20 parts of water and 270 parts of glacial acetic acid in such manner that the temperature does not rise above 3° C. The whole is stirred for a short time longer at 0° C., and unconsumed chromium trioxide is then decomposed with sodium bisulfite solution. After evaporation under reduced pressure, the whole is dissolved in water and extracted with a mixture of ether and chloroform. The ether-chloroform solutions are then washed with caustic soda solution and water, dried, and evaporated. The residue contains progesterone, and, in order to isolate the latter, the residue is dissolved, for example, in 100 parts of benzene and extracted several times with sulfuric acid of 50 per cent. strength. The sulfuric acid solutions are diluted with water, extracted with ether, and the ethereal solutions are washed neutral with caustic soda solution and water. After drying and evaporating, the crude progesterone remains behind. By recrystallization from ether or isopropyl ether there are obtained therefrom about 2.34 parts of pure progesterone having the double melting point 120° C. and 129° C. This represents a yield of 42.7 per cent. of the theoretical yield calculated on the Δ^{23}-3-acetoxy-5-chloro-24:24-diphenyl-cholene which undergoes reaction.

If, on the other hand, the bromination with bromosuccinimide is conducted without the aid of light, only a small fraction of the substance enters into reaction even when a three-fold excess of bromosuccinimide is used, and the final yield, when starting material recovered is taken into account, amounts at best to 12 per cent. but is generally considerably less.

Good yields are also obtained with other sources of light, for example, a luminous arc lamp or a mercury vapour lamp, or with the use of bromophthalimide instead of bromosuccinimide.

Example 2

The quantity of crude $\Delta^{5,20,23}$-3-hydroxy-24:24-diphenyl-cholatriene obtained from 10 parts of Δ^{23}-3-acetoxy-5-chloro-24:24-diphenyl-cholene in the manner described in Example 1 is dissolved in warm hexane, and the solution is cooled, whereupon the crystalline triene slowly separates. From hexane there are obtained crystals melting at 136–140° C., and from rectified spirit needles melting at 162–166° C. A further quantity of the triene can be isolated, for example, by chromatographing the mother liquors dissolved in hexane over aluminium oxide. A total of 5.7 parts of pure crystals are obtained, representing a yield of 66.4 per cent. of the theoretical yield.

2 parts of the triene are oxidized by means of 20 parts of cyclohexanone in toluene as described in Example 1. The resulting keto-compound is recrystallized from ethanol, and is thus obtained in a voluminous condition. It is dried under reduced pressure at 60–80° C. The pure $\Delta^{4,20,23}$-3-keto-24:24-diphenyl-cholatriene melts at 106–110° C. The yield of the pure ketone amounts to about 1.8 parts.

Example 3

The $\Delta^{4,23}$-3-keto-24,24-diphenyl-choladiene used as starting material in this example is prepared, from Δ^{5}-3-hydroxy-cholenic acid methyl ester, for instance, as follows: The latter is first caused to react, by Grignard's method, with phenyl-magnesium-bromide to form Δ^{5}-3,24-dihydroxy-24,24-diphenyl-choladiene. The tertiary hydroxyl group in 24-position is then split off with the aid of iodine in boiling benzene solution to obtain the $\Delta^{5,23}$-3-hydroxy-24,24-diphenyl-choladiene of melting point 177–180° C., which is dehydrogenated in a boiling mixture of toluene and cyclohexanone in the presence of aluminium-iso-propylate. By recrystallization from ethanol there is obtained $\Delta^{4,23}$-3-keto-24,24-diphenyl-choladiene melting at 139–140°.

2 parts of $\Delta^{4,23}$-3-keto-24,24-diphenyl-choladiene and 0.72 part of N-bromosuccinimide are covered with 50 parts by volume of carbon tetrachloride. The mixture is boiled for 15 minutes while being exposed to light from a strong incandescent lamp and cooled before the formed succinimide is filtered off with suction. The clear filtrate contains the $\Delta^{4,23}$-3-keto-22-bromo-24,24-diphenyl-choladiene. It is mixed with 10 parts by volume of dimethyl-aniline, the carbon tetrachloride is removed by distillation and the residual solution boiled for 10 minutes, cooled and diluted with ether. The ether-solution is washed with dilute hydrochloric acid and water, dried and evaporated. The residue is taken up in ethanol and treated with some activated charcoal. When the filtered solution is concentrated by evaporation, the $\Delta^{4,20,23}$-3-keto-24,24-diphenyl-cholatriene crystallizes, which after recrystallization melts at 106–110° C. It is identical with the product of Example 2.

1 part of $\Delta^{4,20,23}$-3-keto-24,24-diphenyl-cholatriene is dissolved in 20 parts by volume of ethylene-chloride and 20 parts by volume of acetic acid of 90 per cent. strength, the solution cooled with ice while being mixed with a solution of

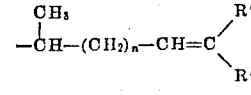
0.5 part of chromium trioxide in 20 parts by volume of acetic acid of 90 per cent. strength, and the whole is allowed to stand for 20 hours at 0° C. It is then cautiously mixed with some sodium bisulfite solution and, after an addition of water, concentrated by evaporation under reduced pressure. The aqueous suspension is extracted by agitation with a 4:1 mixture of ether and chloroform, the ether-chloroform solution washed with dilute sodium carbonate solution and water, dried and evaporated. The residue is dissolved in 50 parts by volume of benzene, the progesterone extracted in per se conventional manner by repeated agitation with sulfuric acid of 50 per cent. strength by volume, the combined resultant sulfuric acid solutions are diluted with water and extracted with ether. The ether solution is washed with dilute caustic soda solution and water, dried and concentrated by evaporation. The progesterone slowly precipitates in the form of crystals and has the characteristic double melting point of 120° C. and 129° C.

Example 4

10 parts of $\Delta^{4,23}$-3-keto-24,24-diphenyl-choladiene and 3.61 parts of N-bromosuccinimide are covered with 200 parts by volume of carbon tetrachloride. The mixture is boiled for 15 minutes with exposure to light from a strong incandescent lamp after which time the mixture is refluxed for 8 hours without special irradiation, hydrogen bromide splitting off. The solution is cooled, the formed succinimide removed by suction-filtering and the filtrate evaporated. The residue is dissolved in warm ethanol, the solution treated with some activated charcoal, filtered and concentrated by evaporation. The resultant $\Delta^{4,20,23}$-3-keto-24,24 - diphenyl - cholatriene melts at 106-110° C. and is identical with the triene described in Examples 2 and 3. When oxidized with chromic acid it yields progesterone, as indicated in Example 3.

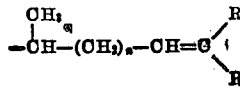
What we claim is:

1. In a process for the degradation of the side chain of a steroid, the step of causing a 10,13-dimethyl - cyclopentanopolyhydrophenanthrene containing an α,β-unsaturated keto group in the nucleus and in 17 position a substituent of the formula



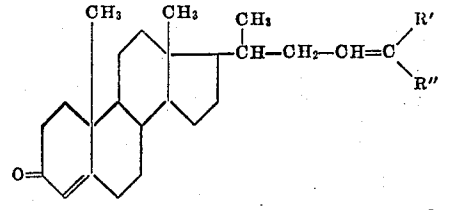
wherein R′ and R″ each stands for a member of the group consisting of hydrogen, lower alkyl and lower aryl radicals and n is one of the integers 1 and 2, to react with a member of the group consisting of a carboxylic acid imide, amide and arylamide halogenated at the nitrogen while exposing the reactants to strong light.

2. A process for the degradation of the side chain of a steroid which comprises treating a 10,13-dimethyl - cyclopentanopolyhydrophenanthrene containing an α,β-unsaturated keto group in the nucleus and in 17 position a substituent of the formula



wherein R′ and R″ each stands for a member of the group consisting of hydrogen, lower alkyl and lower aryl radicals and n is one of the integers 1 and 2, to react with a member of the group consisting of a carboxylic acid imide, amide and arylamide halogenated at the nitrogen while exposing the reactant to strong light, eliminating hydrogen halide from the product thus obtained and subsequently splitting up the newly formed conjugated double bond.

3. A process for the degradation of the side chain of a steroid of the formula



wherein R′ and R″ each stands for a member of the group consisting of hydrogen, lower alkyl and lower aryl radicals and n is one of the integers 1 and 2, comprising treating such steroid to react with a member of the group consisting of a carboxylic acid imide, amide and arylamide halogenated at the nitrogen while exposing the reactant to strong light, eliminating hydrogen halide from the product thus obtained and subsequently splitting up the newly formed conjugated double bond.

4. A process according to claim 3, wherein the elimination of hydrogen halide is effected by means of a dehydrohalogenating agent.

5. A process according to claim 3, wherein the elimination of hydrogen halide is effected by simple heating.

6. A process according to claim 3, wherein the splitting up of the newly formed conjugated double bond is effected by chromium oxide.

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Certificate of Correction

Patent No. 2,461,912. February 15, 1949.

KARL MIESCHER ET AL.

It is hereby certified that errors appear in the printed specification of the above numbered patent requiring correction as follows:

Column 5, line 57, for "3-positions" read *3-position*; column 9, line 59, claim 1, for "arlylamide" read *arylamide*;

and that the said Letters Patent should be read with these corrections therein that the same may conform to the record of the case in the Patent Office.

Signed and sealed this 16th day of August, A. D. 1949.

[SEAL]

THOMAS F. MURPHY,
Assistant Commissioner of Patents.