

UNITED STATES PATENT OFFICE

2,142,170

CYCLOPENTANE-POLYHYDROPHENANTHRENE DERIVATIVES

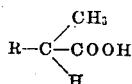
Max Bockmühl, Gustav Ehrhart, Heinrich Ruschig, and Walter Aumüller, Frankfort-on-the-Main-Hochst, Germany, assignors to Winthrop Chemical Company, Inc., New York, N. Y., a corporation of New York

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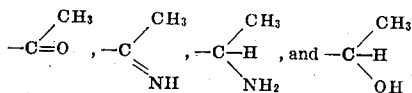
3 Claims. (Cl. 260—397)

The present invention relates to cyclopentane-polyhydrophenanthrene derivatives.

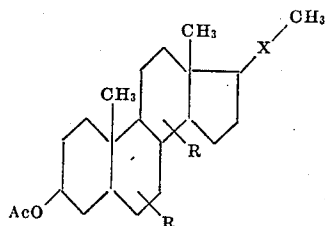
In U. S. application Serial No. 49,644, filed November 13, 1935, in the name of Max Bockmühl, Gustav Ehrhart and Heinrich Ruschig, there is described a manufacture of ketones from the acids of the formula



in which R stands for a tetracyclic hydro-aromatic ring system. According to this process in the course of which transformations occur in the ring 1 of the cyclopentane-polyhydrophenanthrene-radical and which is of importance for the preparation of sterol-like bodies there are obtained for instance sterol-like compounds with the side chains:



On further investigating this field it has been found that intermediate products or final bodies important in sterol chemistry are obtained by subjecting to a partial saponification compounds of the following general formula:



wherein

Ac stands for an acyl residue, at least one

R stands for an acyloxy-residue whereas the second

R may stand for hydrogen and

X stands for a carbon atom with a bivalent residue, such as $\text{C}=\text{O}$, $\text{C}=\text{NH}$ or with a secondarily bound $-\text{NH}_2$ -group or $-\text{OH}$ -group, such as CHNH_2 or CHOH ,

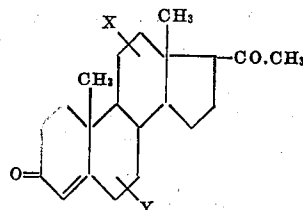
oxidizing the compounds of 3-hydroxy-cyclopentane-polyhydrophenanthrene thus obtained, halogenating the ketones produced, splitting off hydrogen halide from the halogen ketones formed and if necessary transforming the secondarily bound amino-group or hydroxy-group in any desired phase of the process into the keto-group belonging thereto.

The process is performed for instance as follows: A derivative of 3:7:12-triacetyl-hydroxycyclopentane-polyhydrophenanthrene with the side chain $-\text{CO}-\text{CH}_3$ in 17-position is carefully saponified, whereby only the ester group standing in 3-position is saponified. The product obtained, possessing a free hydroxyl group in 3-position, may now be oxidized to form the keto-group and the ketone obtained may be halogenated, whereby the halogen enters into ortho-position to the 3-keto-group. By the separation of hydrogen halide a double bond is produced in the neighbouring position to the keto-group.

If in the 17-position of the cyclopentane ring there is present, instead of the keto-group, a ketimide-group or a secondary hydroxy-group or amino-group, there may advantageously be made from these compounds first substances with a side chain of the ketone character and then the ketones obtained may be subjected to the course of the manufacture described. With the same or a similar success the ketimide-compounds, hydroxy-compounds or amino-compounds named may be transformed in another desired phase of the process into the compounds with a corresponding keto-side chain.

The side chains with the groups CNH , CHOH and CHNH_2 may be transformed into the ketones belonging thereto by known methods, for instance by transforming the amino-group by means of HNO_2 into the corresponding secondary alcohol and transforming the latter into the ketone by oxidation with chromic acid; the ketimide groups are converted into the corresponding ketones by saponification and separation of ammonia.

The process described above leads to compounds of the following general formula:

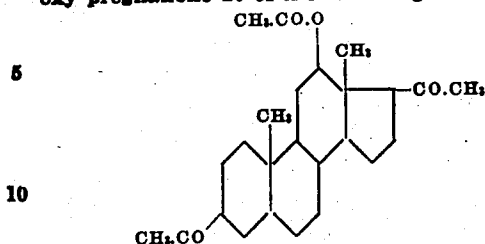


wherein

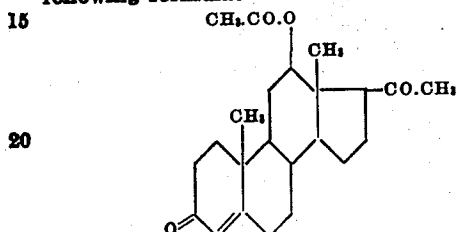
X stands for hydroxyl or an acyloxy residue and Y stands for hydrogen, hydroxyl or an acyloxy residue.

All these products are colorless crystals which readily dissolve in alcohol and chloroform but which sparingly dissolve in water.

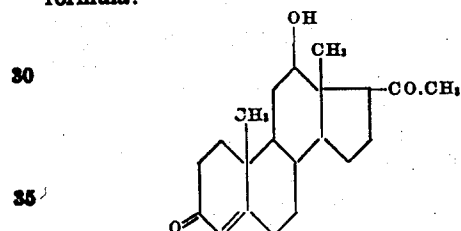
The process which starts from the 3:12-diacetoxy-pregnanone-20 of the following formula:



and leads to the 12-acetoxypregesterone of the following formula:



and by saponifying the last-named compound to the 12-hydroxypregesterone of the following formula:



has proved to be especially important.

The compounds obtained according to the invention may be used as medicinal remedies or for the manufacture of such remedies.

The following example serves to illustrate the invention but it is not intended to limit it thereto:

(a) 3:12-diacetoxypregnanone-20

7.8 grams of dihydroxypregnanone-20 together with 30 cc. of anhydrous pyridine and 30 cc. of acetic anhydride are heated for about 36 hours in the boiling water bath. The whole is evaporated to dryness under reduced pressure, the brown residue is dissolved in ether and the ethereal solution is repeatedly washed with dilute sulfuric acid, soda solution and water. The ethereal solution is then dried by means of sulfate and concentrated. The residue obtained is a light-brown resin which could not be crystallized. The yield amounts to 9.5 grams of raw product.

(b) 3-hydroxy-12-acetoxypregnanone

4 grams of the crude diacetyl compound are dissolved in 150 cc. of methanol and 50 cc. of 2N-caustic soda solution are added thereto. The mixture is allowed to stand for ¾ hour at room temperature and is then cautiously acidified by means of dilute sulfuric acid. A magma of fine needles separates. It is dissolved in ether, the ethereal solution is washed with sodium carbonate and water, dried by means of sodium sulfate and concentrated. Crystallization sets in if the residue is rubbed with ether. The impurities contained in the residue are taken up by the ether and pure white crystals are obtained melting at 203° C. The yield amounts to 2.1 grams.

(c) 12-acetoxypregandione-3,20

2 grams of 3-hydroxy-12-acetoxypregnanone-

20 are allowed to stand for 12 hours at room temperature in a mixture of 50 cc. of glacial acetic acid, 600 milligrams of chromic anhydride and a small quantity of water. The whole is rendered feebly alkaline by means of a dilute lye extracted with ether and after having been washed with water the ethereal solution is dried with sodium sulfate. After distillation there are obtained 1.8 grams of 12-acetoxypregandione in the form of a resin which crystallizes by rubbing it with ether or petroleum ether. From dilute methanol the diketone is obtained in the form of needles melting at 132.5° C.

(d) 12-acetox-4-bromo-pregandione-3,20

1.8 grams of the crude pregnandione are dissolved in 30 cc. of glacial acetic acid and after the addition of some drops of hydrobromic acid 5 cc. of a molal solution of bromine in glacial acetic acid are added drop by drop. Each drop of the bromine solution is immediately consumed. The solution is poured into water and the separated flakes are filtered with suction, dissolved in ether and dried. By rubbing at the inside of the vessel with a glass rod crystals separate from the ethereal solution which melt at 170° C. while decomposing. The yield in crystallized acetoxy-bromopregandione amounts to 1 gram.

(e) 12-acetoxypregesterone

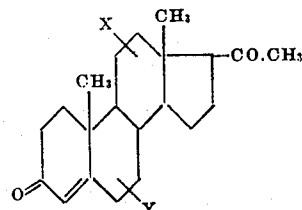
1 gram of 12-acetoxy-4-bromo-pregandione-3,20 is boiled with 50 cc. of anhydrous pyridine for about 16 hours in a reflux apparatus. The light yellow solution is poured into dilute sulfuric acid and the crude raw acetoxy-pregesterone is isolated by extracting with ether. The product obtained after the distillation of the ether is free from bromine and crystallizes when being rubbed with ether. The ethereal solution is decanted, the crystals are dissolved in methanol, the solution is boiled with animal charcoal, filtered with suction and water is cautiously added. The acetoxy-pregesterone crystallizes in the form of needles and after having been redissolved once more it melts at 181° C. The yield amounts to 500 milligrams of an analytically pure product.

(f) 12-hydroxypregesterone

400 milligrams of 12-acetoxypregesterone are saponified by boiling them for one hour with 5 cc. of 1.1 N-methylalcoholic caustic potash solution. After having been recrystallized from methanol the 12-hydroxypregesterone melts at 195° C. It crystallizes in the form of colorless hexagonal prisms. The yield is nearly quantitative.

We claim:

1. The compounds of the following general formula:

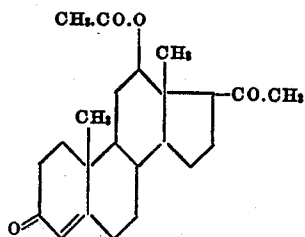


wherein

X stands for a member of the group consisting of hydroxyl and an acyloxy residue and Y stands for a member of the group consisting of hydrogen, hydroxyl and an acyloxy residue,

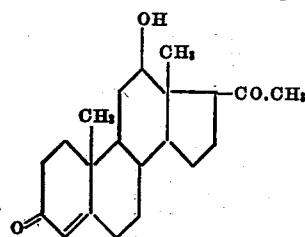
said compounds being colorless crystals readily soluble in alcohol and chloroform and sparingly soluble in water.

2. The compound of the following formula:



said compound forming colorless crystals readily soluble in alcohol and chloroform and sparingly soluble in water, melting at 181° C.

3. The compound of the following formula:



said compound forming colorless crystals readily soluble in alcohol and chloroform and sparingly soluble in water, melting at 195° C.

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