Cl. 260

Published Apr. 20, 1943

Serial No. 144,097

ALIEN PROPERTY CUSTODIAN

PROCESS FOR OXIDISING UNSATURATED POLYCYCLIC ALCOHOLS

Rupert Oppenauer, Amsterdam, The Netherlands; vested in the Alien Property Custodian

No Drawing. Application filed May 21, 1937

The chemical investigation of hormones has shown in the last years that a great number of these physiologically and pharmacologically so important substances and particularly the sex-hormones are polycyclic ketones. It has been found e. g. that progesteron which is the active substance of the corpus luteum extracts is Δ-4,5 pregnendion (3,20) and that testosteron is Δ-4,5-androstenol-(17)-on-(3). These and many other hormones which are polycyclic ketones were also prepared by synthetic way from cholesterol, stigmasterol etc. since long, such as, e. g. the progesteron (Butenandt and cooperators Z. Physiol. Chem. 227, 84, 1934, Ber. 67 B, 1611, 2085, 1934 and Fernholz Ber. 67, 1855 2027, 1934), the testosteron (Ruzicka and cooperators Helv. Chim. Acta 18, 1264, 1478, 1935), the methyltestosteron (Ruzicka, Goldberg Rosenberg Helv. Chim. Acta 18, 1487, 1935), the androstendion (Ruzicka, Wettstein, Helv. Chim. Acta 18, 986, 1935) etc.

As starting materials for the preparation of polycyclic ketones such as the above mentioned ones, containing beside a keto-group a double bond substances were used in the already known processes which substances, leaving out of consideration possible sidechains, have a hydroxilic group to C_3 and a double bond between C_5 and C_6. These substances have consequently to undergo during one stage or the other of the synthese the same chemical changes taking place in the preparation of cholestenon from cholesterol.

For effecting this last mentioned reaction two processes have been described. Diels (Ber. 37, 3099, 1904) has melted together cholesterol and cupric oxide at 280–300° C. and obtained in this way cholestenon in a yield of 65%. On the other hand Windaus and Abderhalden (Ber. 39, 518, 1906) added to the double bond of the cholesterol the calculated quantity of bromine, oxidised the dibromide to the dibromoketone by means of $KMnO_4$ or CrO_3 and then eliminated again the bromine from this dibromoketone; they also obtained in this way a yield of cholestenon of 60 to 65%. Both processes have already been applied for the preparation of polycyclic ketones from alcohols such as e. g. the oxidation by means of CuO according to Diels in connection with the progesteron (Fernholz B. 67, 2030, 1934). In this way, however, only a yield of 4% was obtained which can be readily understood bearing in mind the drastic treatment.

The second process (via the bromine derivatives) is the method generally in use up till now for the synthesis of polycyclic unsaturated ketones. In this way crystallized progesteron e. g. was obtained from Δ-5, 6-pregnenol-(3)-on-(20) in a yield of 35–40% (Butenandt B. 69, 443, 1936). This method was also applied for the preparation of testosteron and methyl testosteron, however with relatively low yields never exceeding 50% (Ruzicka, loc. cit.). These great losses are due, on the one hand, to the complicated reaction (2 intermediary products) and on the other hand all optimal conditions must be taken into consideration as exactly as possible when executing these reactions, which conditions are, however, different from one case to the other. (vide Butenandt Ber. 67, 2087, 1934), Fernholz (Ber. 67, 2029, 1934).

Other processes for economically effecting the oxidation are unknown up till now. It is true that Schönheimer (J. Biol. Chem. 110, 461, 1935) has described a modification of the last mentioned process in which he obtains cholestenon in a good yield starting from the cholesterol dibromide (the intermediate product of bromination). In this way, however, the losses during the whole reaction are only partly avoided and, moreover, this method is not applicable with the same successful result to substances which may be prepared by my process.

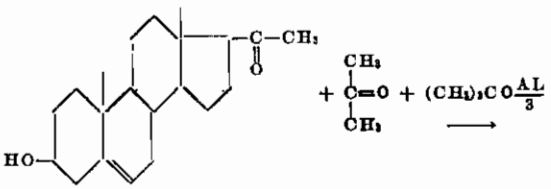
The object of my invention is to effect this oxidation in a completely new and extraordinarily simple way whereby a substantially quantitative yield is obtained. I have found that unsaturated polycyclic alcohols are capable of yielding 2 atoms of hydrogen per molecule and per hydroxilic group to other substances involved in this reaction and containing keto groups under the influence of certain alcoholates. In this way e. g. the compounds of the cholesterol type are oxidised to those of the cholestenon type and as a matter of fact in such a delicate way that the yield is practically the theoretic one.

My new process is in every respect superior to the methods known till now. My process consists herein that the sterol alcohol to be oxidised is treated in presence of tertiary metal alcoholates, preferably tertiary alcoholates of the aluminium or the magnesium chloride with an excess of hydrogen acceptor. Preferably the reaction is carried out at an increased temperature (50–140° C.) in order to increase the reaction speed, and, moreover, in order to increase the sulability of the intermediary reaction products an indifferent solvent, such as benzene may be added.

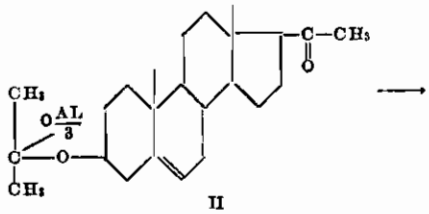
As hydrogen acceptors I may use ketones and aldehydes of the aliphatic, alicyclic and aromatic series.

Without binding my process to a specific theory

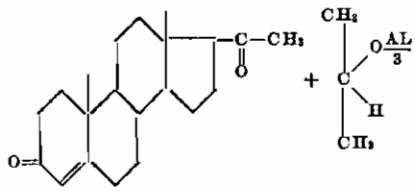
I suppose that the reaction takes place in such a way that from the polycyclic alcohol (I) e. g. with acetone under the action of the aluminium respectively magnesium alcoholate an addition compound (II) is formed which splits into the α,β-unsaturated ketone (III) and propyl alcohol.



I
Pregnenolon



II



III
Progesteron

My method may be applied to unsaturated polycyclic oxy ketones (e. g. dehydroandrosteron, pregnenolon, etc. which are oxidised in this way to diketones), as well as to unsaturated polycyclic oxi-esters (e. g. the acetate-(17) of the androstendiol) besides to sterol alcohol (e. g. cholesterol). It was particularly surprising that the ester group of the oxi-esters is not saponified during this operation since it was known that esters as a rule react with alcoholates under saponification (vide Windaus and cooperators Ann. 520, 100, 1925). Also the presence of a tertiary OH-group in the molecule is not objectionable in my process so that it is possible to prepare by my method e. g. methyl testosteron from 17-methyl androstendiol-(3,17) in a substantially theoretic yield (compare Ruzicka Helv. Chim. Acta 18, 1487, 1935). By means of my new method special substances can be prepared by synthesis which could not be made up till now, due to the fact that during the drastic oxidation of substances having several double bonds, secondary reactions take place in the known methods. E. g. the ergostatrienon could not yet be prepared till now and its synthesis with a very great yield according to my new process is described in example 5. For carrying the aluminium or magnesium chloride to the hydrocilic groups to be oxidised, tertiary alcohols come mainly into consideration, such as e. g. trimethyl carbinol, amylene hydrate, triphenyl carbinol.

The progress obtained by my new process consists herein that:

1. The yields are approximately twice as high as in the known processes.

2. The reaction can be effected very simply and requires only a very short reaction time in comparison to the known methods.

3. The method can be applied to crude concentrates with the same success. E. g. a progesteron concentrate can be prepared from the mother liquors of the ketones obtained during the manufacture of the dehydro androsteron from cholesterol or sitosterol and this was technically absolutely impossible till now.

The unsaturated polycyclic ketones prepared in this way may be applied in therapeutics.

My invention is elucidated by but not at all restricted to the following examples:

1. Preparation of cholestenon from cholesterol. 10 grams of cholesterol are dissolved in 100–150 cm³ of acetone under heating and a solution of 20 grams of tertiary aluminium butylate in 300 cm³ of anhydrous benzene is added hereto. This mixture is heated under reflux cooling during 7 hours; the aluminium is removed by shaking out with diluted sulphuric acid, the benzene layer is washed with water, dried with sodium sulphate and then evaporated to dryness. Substantially pure cholestenon remains behind which is obtained in crystallized form by recrystallization, e. g. from methanol in a yield of 90–95% of the theory.

2. Preparation of androstendion from dehydroandrosteron, 2 grams of dehydroandrosteron are heated under reflux cooling with 2 grams of aluminate of the amylene hydrate and 80 grams of acetophenone in 150 cm³ of benzene during 14 hours. One hydrolizes then with diluted sulphuric acid and the washed and dried benzene solution is evaporated to dryness. The residue is fractionally distilled in high vacuum (cathode-vacuum) and the fraction distilling over at 120–140° C. is recrystallized from ether. Androstendion (melting point 170–172° C.) is obtained in a yield of 80–86% of the theory.

3. Preparation of methyl testosteron from methyl androstendiol. 0.6 gram of 17-methyl Δ-5.6 androstendiol (3,17) is heated under reflux cooling during 20 hours in 50 cm³ of benzene and 12 cm³ of acetone with 3 grams of tertiary chloro magnesium butylate, which may be prepared by conversion of acetone with methyl magnesium chloride. The further treatment takes place as in Example 1 and methyl testosteron (melting point 160–162° C.) is obtained in a yield of more than 75% of the theory.

4. Preparation of testosteron from androstendiol. 0.7 gram of 17-mono acetate of the androstendiol (3,17) is heated under reflux cooling in 30 cm³ of toluene and 8 cm³ of acetone with 1 gram of tertiary aluminium butylate during 5 hours. The further treatment takes place as in Examples 1 and 2 and testosteron acetate (melting point 135–139° C.) is obtained in a yield of 80–90% of the theory.

5. Preparation of ergostatrienon from ergosterol. 1.5 grams of ergosterol are dissolved under heating in 120 cm³ of gasoline (boiling point 100–125° C.) and heated under reflux cooling after addition of 20 grams of acetone and 1 gram of tertiary aluminium butylate during 8 hours. The further treatment is effected as in Example 1, and 1.12 grams of crystallized ergostatrienon (M. P. 131–132.5° C.) are obtained as needles.

RUPERT OPPENAUER.