ANODIC OXIDATION OF CHOLESTEROL DERIVATIVES.

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With 1 Figure in the text.

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It is known that in the oxidative disintegration of certain derivatives of cholesterol, as well as in oxidation of the side chain, there are produced keto-alcohols and di-ketons belonging to the group of sexual hormones, or other substances valuable as starting products in the synthesis of sexual hormones.

It is also known that oxidation of the side chain takes place with the usual oxidative materials (chromic acid and potassium-permanganate).

In the following we describe a procedure in which the oxidation takes place electrolytically, i. e., with nascens oxygen, developed anodically.

Electrolytical oxidation as a method in preparative sterol chemistry is not extensively worked out. Its use is, however, desirable as it enables experimental conditions to be varied largely, and it seems likely that with its help oxidation, especially of large molecules, where the oxidation is not one-sided, could be studied more elaborately.

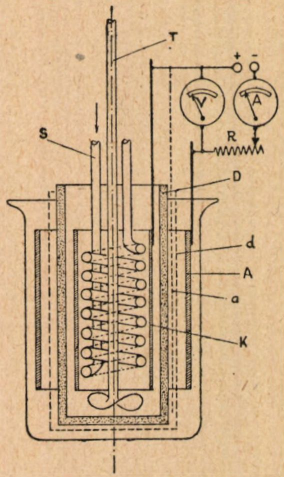
Naturally anodic oxidation of cholesterol derivatives is not one-sided. By the splitting off of the side chain other oxidative products (aldehydes, carbonic acids) besides ketons and keto-alcohols are produced. As the procedure we describe in the following is concerned with the production of ketons created by the splitting off of the side chain, a consideration of the other oxidative derivatives falls outside the scope of this work.

As regards practical use, according to the experiments so far performed, production does not exceed, indeed in some cases is less than, that of other methods. Therefore the experiments published here should be considered chiefly as informative. They are the basis of work in progress, which is concerned with the study of the mechanism of oxidation.

During the course of the experiments saturated and unsaturated steroid ketons were produced.

From the saturated ketons we succeeded in preparing 3-acetoxi-etio-allo-cholanone and androsterone, the former from acetate of dihydrocholesterol the latter from acetate of epi-dihydrocholesterol, the isolation of both products in its semi-carbazone form.

From the unsaturated ketons, worthy of mention may be dehydroandrosterone, which can be made by the anodic oxidation of cholesterylacetate-dibromide.



The experimental set-up is shown in Figure 1.

The anolyte is put in the clay diaphragm (D) and the catholyte in the outer glass container.

The conduction of the cell is ensured by the introduction of an electrolyte which has great conduction capacity and is indifferent from the point of view of oxidation.

In some cases, especially during the oxidation of saturated sterols there is the disadvantage that the pores of the diaphragm (D) become clogged with the material we are oxidizing. This greatly increases the electric resistance of the cell and hinders long-lasting electrolysis, or makes it altogether impossible. In such cases it is desirable to surround the diaphragm containing the anolyte with another electrolyte separated by a second diaphragm (d) of the same charge. The second diaphragm is immersed in the catholyte. The charge is supplied by a second electrode (a) connected to the anode. By transforming the cell a this way the clogging of the diaphragm generally does not occur.

The size of the electrodes (A and K) are determined by the size and charge of the cell.

The cell becomes very warm during the electrolysis. To avoid overheating, or to ensure an even temperature, we employ an inner cooling system.

The anolyte is stirred during electrolysis by a motor.

The electric charge of the cell is regulated by a resistance (R) and measured by an ampere-meter (A).

The potential difference between the electrodes is shown by a volt-meter (V).

From these potential differences we can determine the resistance of the cell. By changing the composition of anolyte and catholyte we generally succed in keeping the resistance low.

The Experiments.

Example 1.

50 g dihydro-cholesteryl-acetate is dissolved in 1500 ml glacial acetic acid, to which is added 150 ml 50% sodium acetate water solution. This mixture is poured into a 2 l clay diaphragm and is electrolysed as anolyte. The danger of the anolyte diffusing towards the cathode space is avoided by surrounding the diaphragm containing the anolyte with another positively charged electrolyte separated by a second diaphragm. The second diaphragm is immersed in the catholyte. In this second, outer diaphragm and in the cathode space the electrolyte employed consits of one weight of 50% sodium acetate water solution and 6 weights of glacial acetic acid.

The electrodes are made in the form of a hollow cylinder, the anode being made of a gold or platinum plate and the cathode of lead. As electrode into the second diaphragm a platinum wire, bent into the form of a circle, is used, the outlet of which is connected to the anode.

The density of the current, on the basis of the surface of the inner anode, is 80—100 milliamperes per cm^2. The temperature of the anolyte is kept around 80°C, by the aid of a cooling spiral of glass. The anolyte is vigorously stirred during electrolysis.

The amount of the current conducted through the system during electrolysis is 2.2 ampere-hours per 1 g of the starting substance. This means that, for example, in the present experiment where the surface of the anode was 150 cm^2 and the strength of the current 12 A, the time taken for the electrolysis was about 9 hours.

Having finished the electrolysis, the two anode solutions are united and condensed to about 300 ml in vacuum. The residue is poured into 2 l water and the resulting substances, forming an oily precipitate, are extracted with ether. This ether solution is washed with 1% NaOH and several times with water, then it is dried and evaporated.

The volatile oxidative products are expelled from the residue with water vapour and the remaining amorphous product is re-dissolved in ether. The ether solution is then dried and evaporated.

We get a light brown substance which contains oxidation products and some unchanged starting material. From this we prepare the semi-carbazone of the 3-acetoxy-etio-allo-cholanone formed during oxidation, by boiling it in alcoholic solution with semi-carbazide-acetate.

The melting point of this product after purification is 260—262°C. Mixture with the same substance differently produced causes no depression of the melting point.

Example 2.

The solution of 50 g epi-dihydro-cholesteryl-acetate in 1500 ml glacial acetic acid is electrolysed as in the first example.

The preparation of the substance produced is also carried out as above. Androsterone formed during the procedure is isolated as semicarbazone. The semi-carbazone purified through re-crystallization does not depress the melting point if mixed with the same substance prepared by chromic acid oxidation.

Example 3.

50 g cholesteryl-acetate dibromide and 250 g water-free potassium acetate are dissolved in 2 l glacial acetic acid. The solution is poured into a clay diaphragm; the anode, which, can be a graphite electrode or a hollow platinum cylinder, is immersed in it. The diaphragm is put into the catholyte.

The catholyte consists of a 1:1 mixture of a 50% sodium acetate water solution and of glacial acetic acid. A lead cylinder is employed as cathode. The density of the current is 80—100 milliamperes per cm^2 of anodic surface.

The temperature in the system increases during electrolysis. The temperature of the anolyte is kept between 80—90°C by cooling.

The starting material precipitating from the anolyte at the beginning gets oily during electrolysis and is later dissolved.

The amount of current employed is 1.6 A per 1 g cholesteryl-acetate dibromide. In the present case, where the surface of the anode was 200 cm^2 the strength of the current was 16 A, the time taken for the electrolysis was 5 hours.

After completing the electrolysis the anolyte is separated and, after adding 30 g zinc powder, is heated on a water bath. The solution is then filtered, the filtrate concentrated to one-fifth in vacuum. The residue is poured into 2 l water and resulting precipitate dissolved in ether. The ether solution is shaken several times with 5% NaOH to free the product of the carbonic acid produced during oxidation. The solution is then dried and evaporated on a water bath. Volatile substances are dispelled from the residue with water vapour and the remaining substance re-dissolved in ether. The solution is then dried and evaporated. 2 g semi-carbazide acetate dissolved in 25 ml alcohol are added to the residue, and the whole boiled on a water bath for some hours.

A precipitate consisting of colourless crystals is formed. This precipitate is washed several times with hot water after filtration. The substance is dehydro-androsterone semi-carbazone which melts after recrystallization from chloroform-methanol at 270—275°C.

To isolate dehydro-androsterone, 100 mg of the carbazone melting at 270—275°C are suspended in the mixture of 2 ml alcohol, 0.5 ml water and 0.1 ml concentrated sulphuric acid. The suspension is boiled on a water bath for one hour. The resulting solution, clear as water, is neutralized with a 20% solution of NaOH and, after the addition of further 0.5 ml alkali, warmed for another half hour over the water bath. The solution is filtered while hot and the filtrate is diluted in twice its volume of water. In cooling the dehydro-androsterone crystallizes in colourless silky needles.

The product is filtered, washed with a little 40% alcohol and dried. The substance thus obtained melts at 142°C. After re-crystallization from petrole-ether (b. p. 65—80°C) the melting point rises to 148°C.

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Remark:

Part of the experiments were carried out with V. Bruckner in the Organic Chemistry Institute of the University of Szeged, partly in the laboratories of the Gedeon Richter S. A. Pharmaceutical Mfg. Co.

See Hungarian Patents Nos 120106, 123574 and 123023.