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ANODIC OXIDATION OF RING A-AROMATIC STEROIDS. CYANATION OF THE AROMATIC NUCLEUS +

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Abstract: The electrochemical oxidation of 3-methoxy-estra-1,3,5(10)-triene-17-one I in methanolic sodium cyanide solution leads to ring A-substitution products II and III and to the addition product IV. This method represents a new way for the direct introduction of a carbon substituent into position 10 of steroids.

It is well-known that estrone and its 3-alkyl ethers easily react with electrophilic reagents to form substitution and addition products /1,2,3/. Methods for the direct introduction of nucleophiles do not yet exist. By the electrochemical "Umpolung" of the reactivity of the substrats it should be possible to introduce nucleophilic groups /4/.

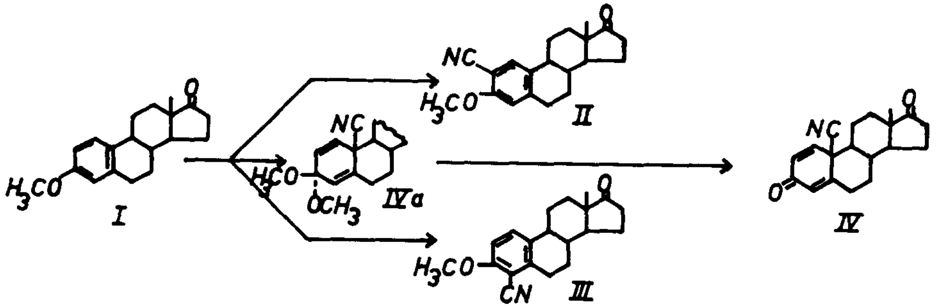
Anodic oxidation of simple phenols like o-, m- or p-methylanisole, which are comparable with I, in the presence of cyanide ions only yielded substitution products and no addition products.

In studying the electrochemical oxidation reaction of compound I in the presence of cyanide ions we found, that the nucleophile can be introduced into position 2,3,4 or 10 of the steroid molecule by substitution and addition reaction, respectively.

The product composition depends on the reaction condition especially on the solvent supporting electrolyte (SSE). In this paper we describe the anodic oxidation of estrone methylether I in a methanolic sodium cyanide solution.

On electrolysis of I (0,0018 mole) in a 0,12 M solution of sodium cyanide in methanol we got three main products, 2-cyano-3-methoxy-estra-1,3,5(10)-triene-17-one II, 4-cyano-3-methoxy-estra-1,3,5(10)-triene-17-one III and 10ß-cyano-estra-1,4-diene-3,17-dione IV in a ratio of 1 : 1 : 2. The anodic oxidation was carried out in an undivided cell between two platinum electrodes (working electrode 70 cm^2, cathode 4 cm^2, distance of the electrodes 1,5 cm) at constant current of 400 mA for 25 minutes.

Compound IVa could not be isolated, because it was hydrolized to IV during working up.



The structure of the substitution products II and III was confirmed by ^{1}H-NMR. Compound IV must be formed by dearomatization of the parent compound. The spectral dates are in correspondence with the addition product, with a 1,4-diene-3-keto-system: IR 2220 cm^{-1} (CN), 1735 cm^{-1} (17-ketone), 1670 cm^{-1}, 1635 cm^{-1} and 1610 cm^{-1} (dienone), UV_{max} 236 nm $\lg \varepsilon = 4,2$. The ß-configuration of the 10-cyano group was determined by CD. The Cotton effects of the cyanodienone IV are the same we got from the literature for 10ß-substituted $\Delta^{1,4}$-3-ketones /3/.

Besides the three main products minor quantities of by-products are formed under the given reaction conditions. In the most important side reaction benzylic methoxylation /7/ followed by nuclear cyanation took place.

As we were especially interested in introduction of a carbon atom at position 10, we tried to minimize the amounts of by-products and substitution products (II and III) in favour of the cyanodienone IV. The best results in this direction we got on electrolysis in a divided cell in a methanolic solution with aquivalent amounts of sodium cyanide. The overall yield on IV was about 60 % but the current yield was to low that further experiments were made under the reaction conditions given above.

For the tranformation of I into IV it is necessary to know , that the electrochemical oxidation must be carried out in the presence of an alcohol or water. With increasing size and branching of the used alcohol the yield of IV decreases. The yield of IV is increased by restricting the o-substitution (II and III) reaction. This is possible by using branched 3-alkyl ethers as parent compounds. In this way the yield of IV could be increased from 30 to 40 %.

On substitution and addition reactions in aprotic solvents, which lead to some other products, will be reported later.

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