N-ACETYL-ε-AMINOCAPROIC ACID. IV. HYDROLYSIS OF N-ACETYL-ε-CAPROLACTAM

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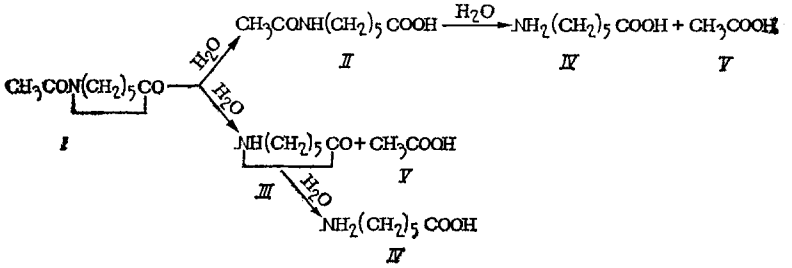
The hydrolysis of N-acetyl-ε-caprolactam (ACL) is one of the major stages in the production of N-acetyl-ε-aminocaproic acid (AACA), an effective pharmaceutical with wound-healing activity [1-3]. It is this stage that is mainly responsible for the comparatively low yield of the end product, 12-16% [3] or 30% [1] of theoretical.

The hydrolysis of acyl lac ams in alkaline solution, which has been examined during work on their polymerization [4-8], proceeds by two pathways, involving either opening of the lactam ring or cleavage of the acyl group. The ratio of the rates of these reactions depends on the number of carbon atoms in the lactam ring, the structure of the acyl group, and the reaction conditions. The acid hydrolysis of acyl lactams has received little attention. Synthetic methods for AACA [1,3] specify that the hydrolysis of ACL be carried out in acidic solution, and specifically in 3% acetic acid.

We set out to develop an efficient process for the production of AAACA by examining the hydrolysis of ACL under various conditions.

The possible pathways for the hydrolysis of ACL are



We used the analytical methods developed earlier [2] to follow the reaction of ACL, since the quantities of each of the five possible components of the reaction mixture can be determined thereby.

As a preliminary we established the probabilities of reactions II → IV and III → IV, which form aminocaproic acid (AA), i.e., we examined the hydrolysis of ε-caprolactam (CL) and AACA.

Figure 1 shows the rate of formation of AA in the hydrolysis of CL and AACA at 100°C. In both cases the reaction is comparatively slow; thus after 4.5 h only 2.7% of the theoretical quantity of AA has been formed by hydrolysis of CL and 1% by hydrolysis of AACA. As we shall show, the hydrolysis of ACL under equivalent conditions is complete after this time.

Thus reactions II → IV and III → IV can be neglected in the first approximation and the major reactions involved in the hydrolysis of ACL can be taken as I → II and I → III.

We examined the hydrolysis of ACL in aqueous solution at 100°C with acetic and sulfuric acids as catalysts. Figure 2 shows that the time to complete reaction depends on the medium acidity. Curves 1 and 2 reveal that the process is autocatalytic, which is the consequence

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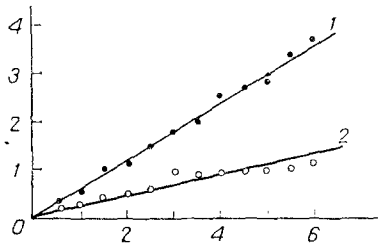

Fig. 1. Formation of AA in the hydrolysis of 1) CL and 2) AACA at 100°C. The abscissa axis is the hydrolysis time (h) and the ordinate axis is the formation of AA (% of theoretical).

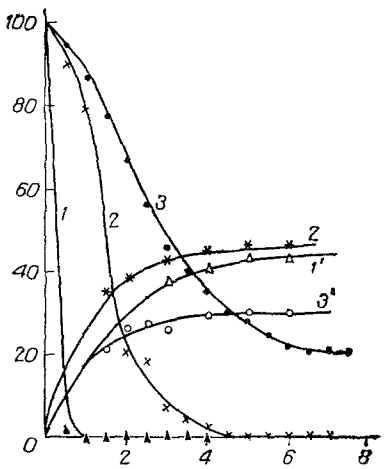

Fig. 2

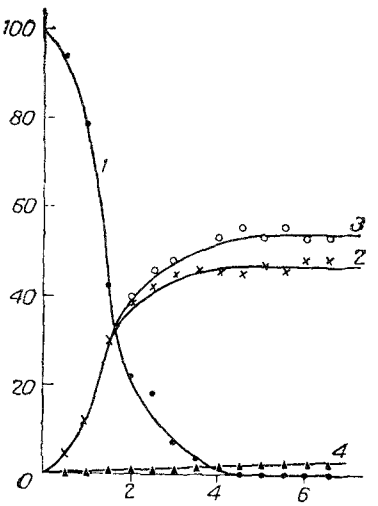

Fig. 3

Fig. 2. Hydrolysis of ACL in the presence of catalysts at 100°C; 1,1') 3% sulfuric acid; 2,2') 3% acetic acid; 3,3') 3% alkali (1 mole ACL per 0.2 mole NaOH); 1,2,3) disappearance of ACL; 1',2',3') formation of AACA. The abscissa axis is the hydrolysis time of ACL (h) and the ordinate axis the percentage hydrolysis of ACL (% of theoretical).

Fig. 3. Hydrolysis of ACL in aqueous solution at 100°C; 1) disappearance of ACL; 2) formation of AACA; 3) formation of CL; 4) formation of AA. The abscissa axis is the hydrolysis time of ACL and the formation of AACA, CL, and AA (h) and the ordinate axis the percentage hydrolysis of ACL and the formation of AACA, CL, and AA (% of theoretical).

of the acidic properties of the reaction products. Thus, if a small quantity of alkali (less than 1 g-eq) is added at the start of the process, the hydrolysis is inhibited by partial neutralization (Figs. 2 and 3). The quantity of AACA formed is not more than 50% of theoretical, i.e., reactions I → II and I → III proceed at roughly the same rate.

Figure 3 shows the results derived when the hydrolysis of ACL was carried out in water without specially added catalysts. Curve 1 of Fig. 3 is almost identical to curve 2 of Fig. 2, which further supports the autocatalytic nature of the process.

Our results show that in this process only about 40-50% of the reactant is consumed in the formation of AACA; the remainder of the ACL is hydrolyzed to CL and acetic acid.

We attempted to change the ratio of the rates of reactions I → II and I → III by carrying out the hydrolysis in mixtures of the discriminating solvents DMF, dimethyl sulfoxide (DMSO), ethanol, acetone, and water. The runs were carried out under standard conditions with a refluxing reaction mixture; the content of the solvent in the water was 30 wt. %.

Figures 4 and 5 show that in all cases the overall rate of hydrolysis is lower than in aqueous solution without additives. The reaction half-life is linearly dependent on the dielectric constant of mixture calculated from [9, 10] (Fig. 6). The ratio of the rates of reactions I → II and I → III is displaced toward the formation of CL and acetic acid.

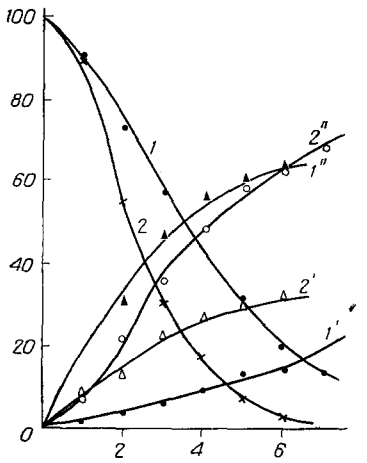

Fig. 4

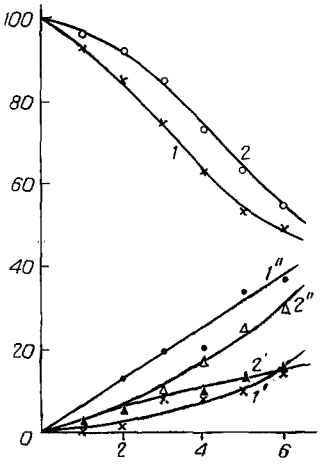

Fig. 5

Fig. 4. Hydrolysis of ACL in mixtures of 1) DMF and 2) DMSO with water; 1,2) disappearance of ACL; 1',2') formation of AACA; 1",2") formation of CL. The abscissa axis is the hydrolysis time of ACL and the formation of AACA and CL (h) and the ordinate axis the percentage hydrolysis of ACL and the formation of AACA and CL (% of theoretical).

Fig. 5. Hydrolysis of ACL in mixtures of 1) ethanol and 2) acetone with water; 1,2) disappearance of ACL; 1',2') formation of AACA; 1",2") formation of CL. The abscissa axis is the hydrolysis time of ACL and the formation of AACA and CL (h) and the ordinate axis is the percentage hydrolysis of ACL and the formation of AACA and CL (% of theoretical).

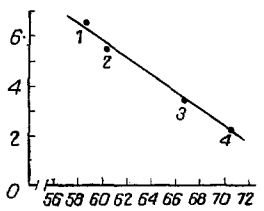

Fig. 6. Dependence of the reaction half-life of the hydrolysis of ACL on the dielectric constant of the solvent mixture. The abscissa axis is the dielectric constant and the ordinate axis the half-life of hydrolysis of ACL (h); 1) acetone–water; 2) ethanol–water; 3) DMF–water; and 4) DMSO–water.

From this experimental study we can conclude that, since the hydrolysis of ACL is an autocatalytic process, it can be successfully carried out in water without special additives. In the hydrolysis of ACL, AACA and CL are formed simultaneously at similar rates. The presence of discriminating solvents reduces the rate of hydrolysis and favors the preferential formation of CL and acetic acid.

On the basis of our results we have developed a process for the production of AACA in which the hydrolysis of ACL is carried out in water without additives and the CL formed in the reaction is recycled [11]. The yield of AACA of at least 98.5% purity by this process is about 50% of the theoretical.

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HYDROXYLATION OF ANDROST-4-ENE-3,17-DIONE BY *Rhizopus Nigricans*

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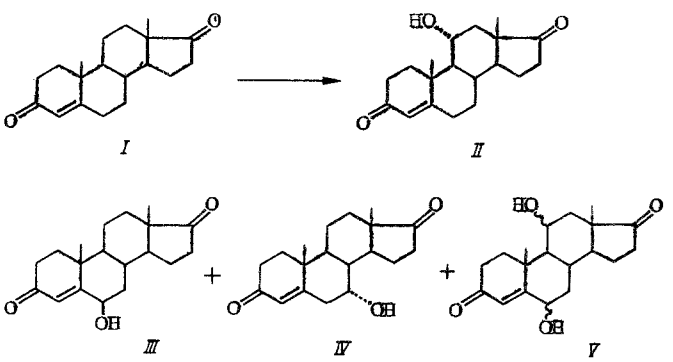
One of the practically important microbiological transformations of steroidal compounds is hydroxylation. It can be applied to compounds of the androstane series [1].

Here we report a study of the conditions of the 11α-hydroxylation of androst-4-ene-3,17-dione (I) by *Rhizopus nigricans* including an examination of the reaction byproducts. We isolated the 7α-hydroxy derivative (IV), whose formation has not been reported in transformations with this fungus.



I II III IV V

We examined the hydroxylation of I by *R. nigricans* and *Tiegemella hyalospora* to select the transforming culture.

We subsequently used *R. nigricans* since it gave twice as much II.

To assess the effect of the mode of introduction of I on the course of the transformation we added it to the beer as a powder prepared with an agate mortar or as solutions in ethanol, acetone, and DMF. The amount of solvent was varied from 3-4% of the mass of the beer in the runs with ethanol and acetone to 0.4-1.4% when DMF was used. We got the best results by adding I in DMF solution with a DMF content in the beer of 1%. The other solvents inhibited the process.

We used medium A with peptone and medium B with cornsteep extract to find the most suitable medium for growing *R. nigricans*. Though the quantity of the biomass grown on medium A was twice that in medium B, we used the same quantity of the mycelium in the transformation. Subsequently we used medium A, since the yield of II was 50% greater than when the fungus was grown on medium B.

To select the transformation medium mycelium slurry was transferred to mains water or to 0.5% glucose solution. Hydrolysis in glucose solution was complete after 24 h (the final pH of the beer was 4.5) while in mains water the reaction had not ended after 46 h (pH 7.3). Hence we subsequently used mycelium slurry in glucose solution.

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