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LETTERS TO THE EDITOR

Synthesis of Imines Based on Orotic Aldehyde and Amino Acids

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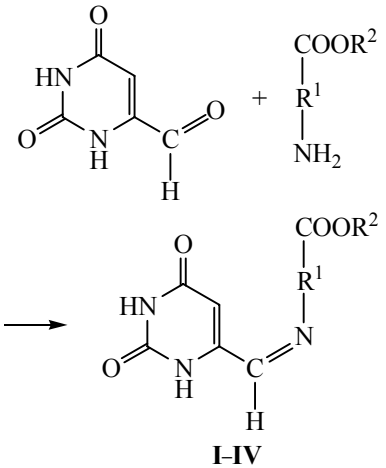
It was shown previously that orotic aldehyde reacted with α-amino acids to form imines having a wide spectrum of biological activity [1, 2]. Therefore a necessity appeared to to study the synthetic opportunities of the orotic aldehyde reactions with acids, their esters and oligomers which also can exhibit a high biological activity.

In this work we investigated the synthesis of imine derivatives by reacting of orotic aldehyde with glycine, esters of ε-aminocaproic and *p*-aminobenzoic acids. One of the possible mechanisms of this reaction is considered.



I–**IV**

I, $R^1 = [(CH_2)_5C(O)NH]_2(CH_2)_5$, R^2 = Bu-*n*; **II**, $R^1 = C_6H_4$-*p*, R^2 = Et; **III**, $R^1 = C_6H_4$-*p*, R^2 = H; **IV**, $R^1 = CH_2$, R^2 = H.

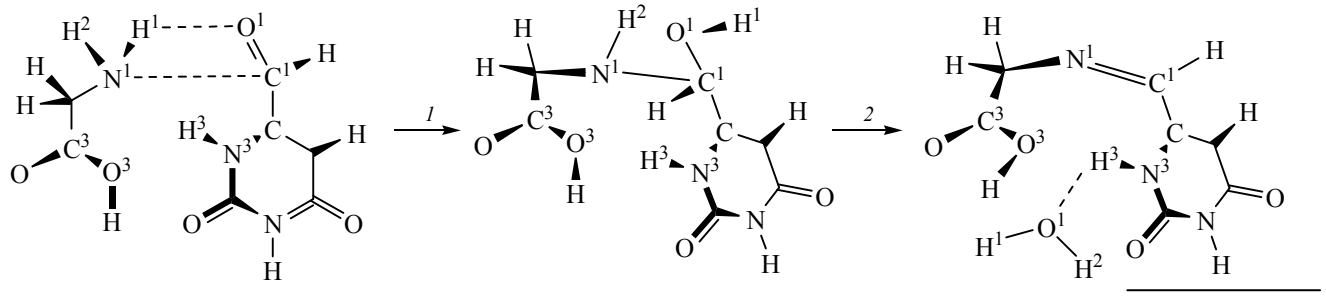
The reaction was carried out in an organic solvent (acetic acid) in the case of esters of amino acids and oligomers or in water (in the case of amino acids). The reaction temperature ranges from 40 to 70°C. Depending on the structure of the starting compounds the yield of imines is 32–81%. The highest yield (81%) was obtained in the case of *p*-aminobenzoic acid, while the lowest (32%), with aminoacetic acid. This is due to the availability of amino group in *p*-aminobenzoic acid and hindrances in the reaction with α-amino acids. The deamination in the case of oligomers of ε-aminocaproic acid leads to an increase in the reaction yield. The structure of imines was confirmed by IR spectroscopy, and the composition was determined by elemental analysis. All obtained imines are yellow crystalline substances with high melting points.

The IR spectra of the compounds obtained contain the absorption bands of amide group at 3288 (N–H), 1716 (C=O), 1636 (amide **I**) and 1540 cm^{-1} (amide **II**), and ester group C=O at 1724 cm^{-1}.

The mechanism of the reaction of orotic aldehyde with aminocarboxylic acids was considered by the example of glycine. Analysis of the possible reaction pathways was performed using quantum chemical method AM1 [3].

The first stage occurs through the formation of four-membered transition state as a result of the approach of the amino group of carboxylic acid to the aldehyde group of orotic aldehyde (there is an interaction between the atoms N^1–C^1 and O^1–H^1). The second stage is dehydration of an intermediate alcohol to form imine.

At the first stage of the reaction there should be overcome the sufficiently high activation barrier (61.3 kcal mol^{-1}) to form the four-membered transition state. The saddle point is reached when the reaction coordinates RN^1–C^1 and RO^1–H^1 are 0.18 and 0.14 nm, respectively. In this connection the reaction should be carried out at a high temperature. Note also that the



reaction is accompanied by a small positive thermal effect (5 kcal mol^{-1}).

The second stage, unlike the first one, is characterized by a lower activation barrier. The saddle point is reached when the reaction coordinate $RH^2–O^1$ (0.13 nm) is located at 53.8 kcal mol^{-1}. This stage is accompanied by a slight negative heat effect (4 kcal mol^{-1}). However, the water release in the second stage leads to irreversible process.

The quantum chemical calculation was performed for the gaseous systems excluding the solvents participation (water, acetic acid), which can reduce the activation barrier and facilitate the reaction progress. The total energy gain during the formation of imine from the reactants is small (1 kcal mol^{-1}).

Thus, the stage determining the formation of iminoesters is the first stage, when the hydroxyl-containing compound is formed. Dehydration of the latter requires less energy and leads to irreversible reaction.

(*E*)-Butyl 6-(6-{6-[(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyleneamino]hexanamido} hexanamido)hexanoate (I). A mixture of 2.57 g (0.0048 mol) of *n*-butyl ester of ε-aminocaproic acid trimer, 25 ml of glacial acetic acid, and 0.56 g (0.004 mol) of orotic aldehyde was refluxed with stirring for 2 h and then cooled to room temperature. The precipitate was filtered off, washed successively with ethanol and diethyl ether to remove the initial reagents, and dried. The reaction products were purified by sublimation in vacuo. Yield 1.1 g (56%), mp 178–180°C. Found, %: C 59.1; H 9.0; N 13.9. $C_{27}H_{45}N_5O_6$. Calculated, %: C 60.6; H 8.4; N 13.1.

(*E*)-Ethyl 4-[(2,6-dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyleneamino]benzoate (II) was prepared similarly. Yield 59%, mp 245°C. Found, %: C 57.8; H 5.0; N 14.9. $C_{14}H_{13}N_3O_4$.Calculated, %: C 58.5; H 4.5; N 14.6.

(*E*)-4-[(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyleneamino]benzoic acid (III) was prepared similarly. Yield 81%, mp 275°C. Found, %: C 55.9; H 4.0; N 16.0. $C_{12}H_9N_3O_4$. Calculated, %: C 55.6; H 3.5; N 16.2.

(*E*)-4-[(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)methyleneamino]acetic acid (IV) was prepared similarly (solvent – water, 80°C). Yield 32%, mp 265°C. Found, %: C 41.7; H 3.7; N 22.5. $C_7H_7N_3O_4$. Calculated, %: C 42.6; H 3.6; N 21.3.

The IR spectra were obtained on a Specord M-82 instrument from mulls in mineral oil.

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