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Formation of Heterocyclic Amino Acids in the Reaction of α,δ- and α,ε-diamino Acids with Nitrosylpentacyanoiron(II)

MIHÁLY T. BECK, ÁGNES KATHÓ, LÁSZLÓ DÓZSA

Institute of Physical Chemistry, Kossuth Lajos University, H-4010 Debrecen, Hungary

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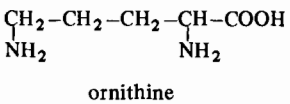
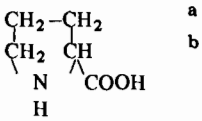
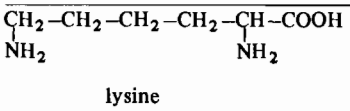
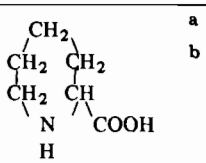
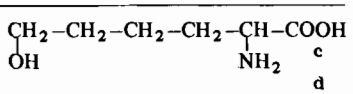
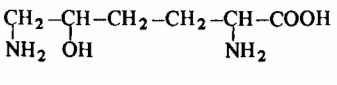
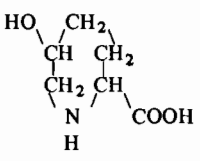
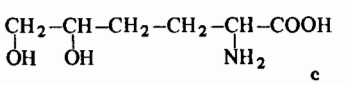
It became recently known that certain nitrosyl complexes are powerful nitrosating agents [1–5]. In contrast with nitrous acid, nitrosation reactions of different organic compounds with these complexes also take place in neutral and even in weakly basic solutions. Probably this feature of these reactions is responsible for the manifold biological activity of nitrosyl complexes [6, 7]. Furthermore this can give a possibility for new methods of transformation of amine containing compounds.

In studying the reactions with amino acids we found that the amino group reacts with different rates depending on its distance from the carboxylic group. *E.g.* the rates are for α-alanine $1.04 \cdot 10^{-7}$ mol dm^{-3} s^{-1} and for β-alanine $22.5 \cdot 10^{-7}$ mol dm^{-3} s^{-1} at pH 9.0; 0.6 mol dm^{-3} alanine and 0.01 mol dm^{-3} complex concentrations, at 25 °C. (Since the rate laws are different the rate constants cannot be directly compared). Therefore it was expected that, when the amino acid contains two amino groups, a selective reaction of the more reactive amino group takes place. In fact, in the reaction of α, δ and α, ε diamino acids ninhidrine active products were detected after the completion of the reaction which indicates amino group in the product. The other important feature is the formation of heterocyclic amino acids. While the simple nitrosation with nitrous acid results in the formation of the corresponding hydroxy compound, the main product of the diazotation of ornithine by the complex is proline, and in the case of lysine, pipecolic acid and ε-hydroxy-norleucine form in about equal amount. The experimental results are summarized in Table I.

It was observed, that no spontaneous cyclization of α-amino, δ-hydroxy or α-amino, ε-hydroxy amino acids occurs in mild conditions [8] even in presence of $Fe(CN)_5NH_3^{3-}$ or $Fe(CN)_5NO^{2-}$. Further-

TABLE I. Products of Reaction of Pentacyanonitrosylferrate(II) with Diamino Acids.

Diamino acid	Cyclic product	Additional product
 ornithine	 proline	a b
 lysine	 pipecolic acid	a b
		 6-hydroxy-2-amino-caproic acid c d
 5-OH-lysine	 5-OH-pipecolic acid	
		 5,6-dihydroxy-2-amino caproic acid c

[a]Detected by paper and thin-layer chromatography (comparing with an authentic compound). [b]Separated in form of N-benzyloxycarbonyl-derivative. [c]Detected by paper chromatography. R_f values are compared with literature data [13, 14]. [d]Two unidentified products detected by chromatography developing with ninhidrine.

more, when the nitrosation reaction is followed by chromatography, it was found that the amount of the hydroxyamino acid does not change according to a maximum curve. These facts clearly show that the hydroxyamino acid is not an intermediate from which the heterocyclic amino acid is formed by ring closure.

The chromatographic experiments show that lysine does not give proline derivates indicating that no formation of free carbonium cation and no hydrogen migration along the carbon chain occurs preceding the ring closure [9]. The observation that no racemization occurs during the reaction indicates that the chiral carbon atom is not involved in the reaction.

Earlier the formation of cyclic amino acids from diamino acids was found in much more drastic conditions with a considerable racemization [10].

Experimental

The reactions were followed by measuring the volume of the dinitrogen evolved and by thin-layer and paper chromatographic analysis of the products using authentic samples.

Reaction with L-ornithine

1.12 g (0.0066 mol) L-ornithine hydrochloride and 2.4 g (0.008 mol) $Na_2Fe(CN)_5NO \cdot 2H_2O$ were dissolved in 40 cm^3 water. The pH of the solution was adjusted to 9.5 and during the reaction was kept at this value with a pH-stater. Vigorous gas evolution occurred, then a small amount of brownish precipitate formed. The reaction was followed by chromatography (Fixion thin layer, 3.3 pH citrate eluent, developing with ninhidrine). The intensity of purple spot of ornithine gradually decreased and that of the yellow spot of proline parallely increased.

Reaction with L-Lysine

The reaction and the analysis of products was carried out similarly as with ornithine.

Developing with ninhidrine one violet and three purple spots appeared on the chromatogram. Developing with isatine a greenish-blue spot appeared with the same R_f as the violet before. Both the color and R_f value is characteristic to pipecolic acid [10]. One of the other products is identified as α-amino, ϵ-hydroxy-caproic acid [12].

Similarly to the proline, but not in the preparative scale, the N-benzyloxycarbonylpipecolic acid also was obtained and identified by IR spectra.

Reaction with 5-OH-Lysine

The method is the same as with ornithine. The reaction products were identified chromatographically. Those are 5-OH-pipecolic acid [10] and 5,6-dihydroxy-2-amino-caproic acid [13].

After completion of the reaction (~6 hrs) benzyloxycarbonyl chloride was added to the solution [11]. The N-benzyloxycarbonylproline was extracted, chromatographically purified (Kieselgel 40 column, chloroform–methanol–acetic acid 45:5:1 eluent) and dried. It was identified by comparison of NMR and IR spectra with authentic material. The yield was 46.3%.*

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