THE STRUCTURE OF THE DIAMINO DICARBOXYLIC AMINO ACIDS FROM THE GLYCOPEPTIDE ANTIBIOTIC RISTOMYCIN A

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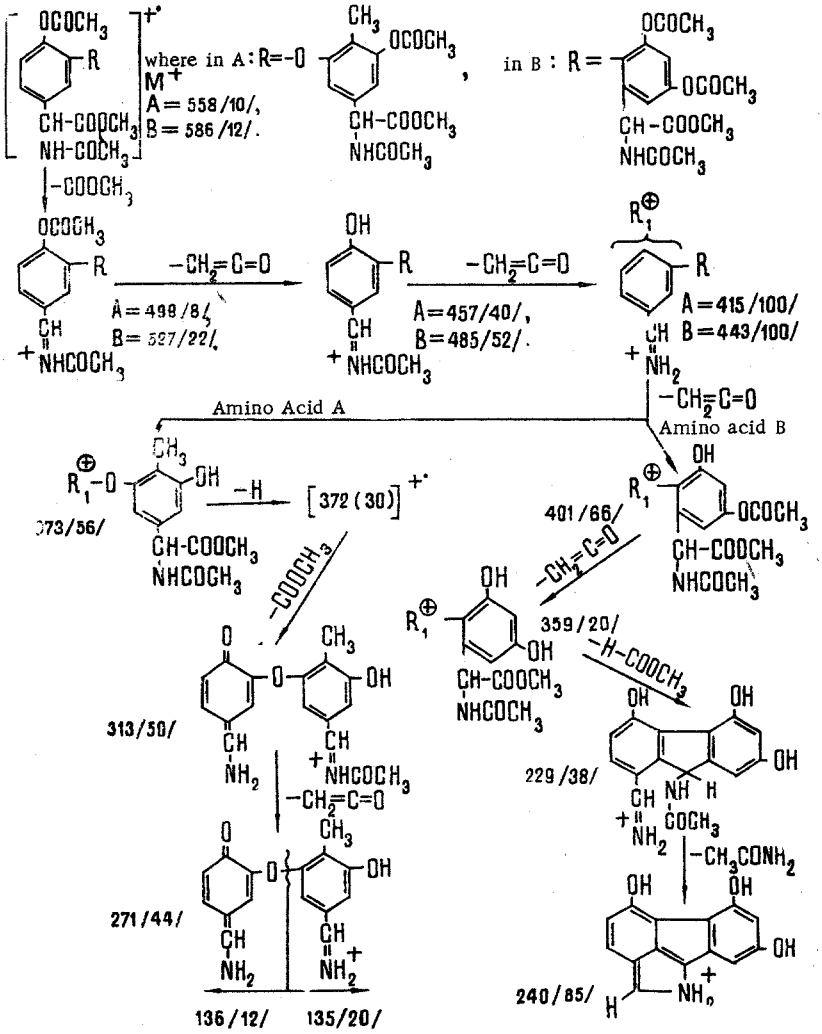
Ristomycinic acid (amino acid A) has been detected previously [1, 2] in hydrolyzates of the antibiotic ristomycin A and ristocetin A, and another amino acid of the glycylphenol type – actinoidinic acid (amino acid B) – has been found in hydrolyzates of actinoidin, ristomycin, ristocetin, and vancomycin [2, 3]. Recently, during an investigation of the structures of the antibiotics ristocetin A and vancomycin, structural formulas have been proposed for amino acid A [4, 5] and for amino acid B [6, 7] differing from those suggested previously [1-3].



Pathways for the possible fragmentation of derivatives of the amino acids ristomycinic acid (A) and actinoidinic acid (B). The figures given are m/e (% of maximum).

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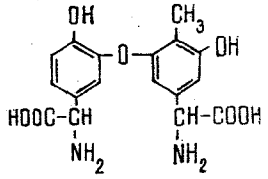
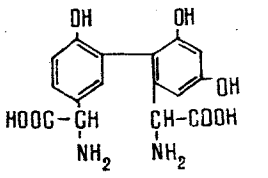
To check the structures of amino acids A and B we have made a mass-spectrometric investigation of their dimethyl esters acetylated at the NH_2 and OH groups with the aid of CH_3OH-Ac_2O (4:1). The completeness of esterification and acetylation was checked by TLC and by electrophoresis at pH 1.1 and 4.2. The mass spectra of the individual compounds were obtained on a Varian MAT-111 instrument with the direct introduction of the substance into the ion source at 92°C and with an energy of the ionizing electrons of 80 eV.

In the mass spectra obtained there are weak peaks of the molecular ions of the derivatives: amino acid A with m/e 558 (10%), corresponding to the molecular formula $C_{27}H_{30}N_2O_{11}$, and amino acid B with m/e 586 (12%), coinciding with the molecular formula $C_{20}H_{30}N_2O_{12}$. The main direction of fragmentation in both cases is the successive splitting out of molecules of ketene from the amine and phenolic groups and the ester groupings ($-COOCH_3$), the maximum peaks in both mass spectra being that of the ion $(M - COOCH_3 - 2CH_2=CO)^+$ with m/e 415 at 443 for the derivatives of amino acids A and B, respectively, which shows the presence in them of the same residue – acetylated p-glycylphenol. However, after the elimination of another – the third – molecule of CH_2CO (from the second glycyl phenol nucleus), differences appear in the nature of the fragmentation of these compounds. Thus, amino-acid A loses a proton and then $COOCH_3$ and a $CH_2=CO$ molecule, after which the ion with m/e 217 begins to break down into ions with m/e 136 and 135 (Scheme), which shows the presence in it of four acetyl groups and an oxygen bridge between phenyl nuclei. Consequently, amino acid A contains two phenolic hydroxyls and, taking into account the characteristics of the PMR spectrum and the synthesis of a derivative of the amino acid from the antibiotic ristocetin [5], it may be considered that ristomycinic acid is 3,3'-diglycyl-5,6'-dihydroxy-6-methyldiphenyl ether, and its structure differs from that suggested previously [1] by the number of phenolic hydroxyls and the arrangement of the substituents in the phenolic nuclei.



Structure of ristomycinic acid

The initial fragmentation of amino acid B is the same as for amino acid A, as far as the ion $(M - COOCH_3 - 3CH_2=CO)^+$ with m/e 401. This ion then decomposes by the successive splitting off of a CH_2CO molecule and of fragments with 60 and 59 amu. Such fragmentation can be explained by the elimination of a proton and a $COOCH_3$ group with the formation of a tricyclic ion having m/e 299 and, finally, the splitting off of a molecule of CH_3CONH_2, which leads to a tetracyclic ion with m/e 240 (see Scheme). The loss of the last-mentioned fragments is possible only if the glycine residue is present in the second, dihydroxyphenyl, part of the molecule in the ortho position to the simple bond of the two nuclei. These results, and also anayltical and synthetic investigations on the structure of the amino acid from vancomycin [6, 7] show that amino acid B (actinoidinic acid) is 2,3'-diglycyl-4,6,6'-trihydroxybiphenyl (see formula) and is not a derivative of diphenyl ether as was previously assumed [3].



Structure of actinoidinic acid

Thus, on the basis of the mass spectra that we have obtained and the literature information the structures of the amino acids ristomycinic acid and actinoidinic acids from the antibiotic ristomycin A have been refined, and they obviously do not differ in structure from the corresponding amino acids from the antibiotics ristocetin and vancomycin.

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