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VIOMYCIN

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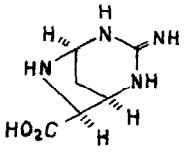
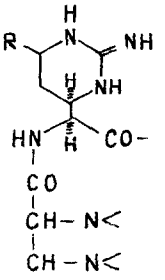
Bycroft, Cameron, Croft, Johnson, Webb and Coggan in their recent publication /1/ proposed II as the partial structure of viomycin, assuming I as the structure of viomycidine. The latter structure was confirmed by synthesis /2/. Our findings indicate a different structure for this antibiotic.

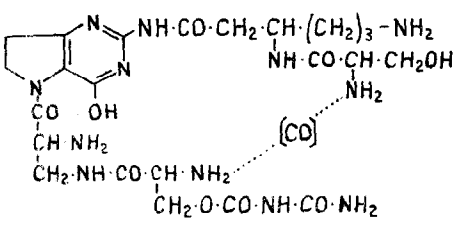


I

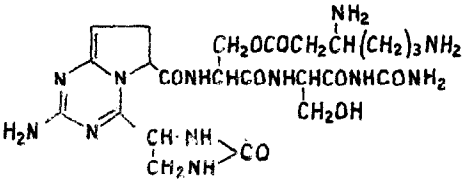


II

Bycroft et al. reported that alkaline hydrolysis of viomycin yielded 2-aminopyrimidine and glycine among other products. We have obtained identical results. For quantitative estimation of 2-aminopyrimidine we have elaborated a special gas-chromatographic technique. In this technique an alkaline solution of viomycin sulphate is introduced directly to the gas-chromatographic column. In hydrolysis of various viomycin preparations the yield of 2-aminopyrimidine was about 14 per cent of the organic matter. According to the structure of viomycin which we are suggesting, the theoretical yield should be 15.4 per cent.



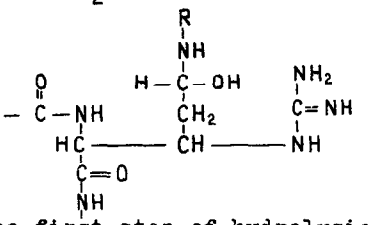
III



IV

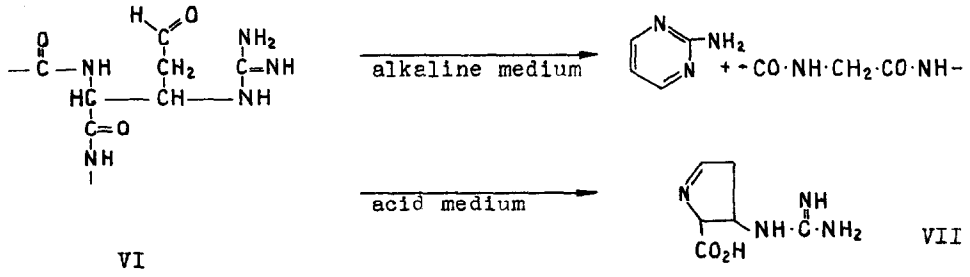
In structure II as well as in structures III and IV proposed for viomycin earlier /3,4/ the guanidine unit exists in cyclic forms.These forms do not readily explain the positive Sakaguchi reaction which viomycin gives. Electrochemical data for viomycin indicate that the strongly basic character of this antibiotic cannot be due to β -lysine amino groups.Furthermore we have found that transamidinase /5/,an enzyme isolated from Streptomyces sp.culture cleaves off the amidine group from viomycin.All these facts strongly suggest the existence of a $-NH\cdot C(:NH)\cdot NH_2$ group in viomycin molecule.

We suggest V,where R= $-CONH_2$ as the partial structure of viomycin



V

We believe that in the first step of hydrolysis the C-N bond of carbinol carbon is attacked.The resulting products are urea and an aldehyde VI[x].In an alkaline medium VI immediately condenses with the amino group of the guanidine unit,the polypeptide group $-CO\cdot NH\cdot CH_2\cdot CO\cdot NH-$ is eliminated,and the system becomes stable by aromatisation to 2-aminopyrimidine.In the suggested partial structure of viomycin also viomycidine,as a product of acid hydrolysis,finds a logical explanation.In an acid medium the $-NH_2$ group of the guanidine unit is ionised and hence the condensation with the -CHO group is less probable.On the other hand,the amino group of the β -guanidino γ -amino α -carboxybutyric aldehyde,having a less basic character,may condense intramolecularly with the aldehydo group.VII is expected to be the final product of hydrolysis.The reaction of the guanidine-carbinol system with the amino group of the glycine fragment,postulated by Bycroft et al.,seems less probable,taking into account the reaction conditions.



VI VII

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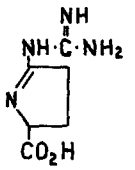
[x]The Fehling test for viomycin is positive.Structures II,III and IV fail to explain this.

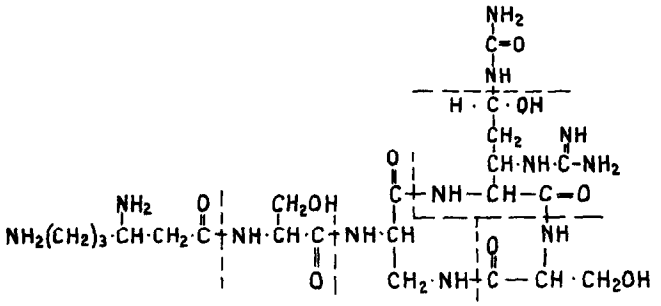
Structure VII and the first structure proposed by Dyer et al. for viomycidine differ only in the position of the double bond.Both structures are not expected to yield aspartic acid in ozonolysis followed by subsequent hydrolysis of the N-acetyl derivative.We believe that this was the reason why Dyer changed his first structure for VIII /6/.



VIII

Much of the physical data and chemical evidence for viomycidine find a logical explanation in reversible transition of VII into I.Examination of Dreidings stereomodels of both structures strongly suggest possibility of such transition.

Taking into account the aminoacid sequence of desureaviomycin as well as the fact that Bycroft et al.found α , β -diaminopropionylglycine in hydrolysis products of viomycin,we suggest IX for the full structure of viomycin.



IX

We believe that structure IX explains why the β -NH_2 group of α , β -diaminopropionic acid in the polypeptide may be free or not free.It also explains why the results of treatment of desureaviomycin with carboxypeptidase[x] may differ.The position of urea in viomycin,as suggested by Kitagawa et al./7/ is not sufficiently supported by experimental evidence.

Kitagawa et al.obtained three different desureaviomycins in which the β -NH_2 group of α , β-diaminopropionic acid was not free /the difference being in R_f and R values as well as in ultraviolet absorption/.Different

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[x]According to Dyer et al.when desureaviomycin was treated with carboxypeptidase one equivalent of serine was released.Kitagawa et al.examining the action of carboxipeptidase on desureaviomycin did not obtain serine.

condensation products of -CHO group with the primary amino group of guanidine unit or the -NH- group bound to the γ -carbon may be responsible for this.

According to Bycroft et al.the guanidine unit of viomycin is unlikely to be concerned with the chromophore.Our work corroborates this hypothesis.We tested several viomycin preparations and we have not found any relation between the ultraviolet absorption /λ =268 mμ/ and the yield of 2-amino-pyrimidine in alkaline hydrolysis of these preparations.

Acknowledgement

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