Communications to the editor

CHEMICAL STUDIES ON TUBERACTINOMYCIN. III

THE CHEMICAL STRUCTURE OF VIOMYCIN (TUBERACTINOMYCIN B)

Sir:

From our chemical studies on the tuberactinomycin group of new peptide antibiotics, we recently proposed total structures for four congeners in this group, tuberactinomycins A, B, N and O.[1] The structure of tuberactinomycin O was conclusively established by X-ray analysis (Fig. 1).[1] All four antibiotics are very similar in biological effects, in amino acid composition as shown in Table 1, and in chemical and physical properties. Therefore we suggested a common amino acid sequence for the four peptides, which differ only in the chemical structure of two amino acid components.[1] The amino acid sequences of tuberactinomycins A and N were determined to be as shown in Fig. 1 from the chemical degradation.[2]

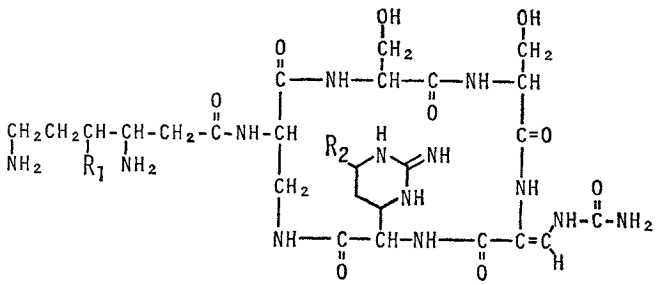
It has been shown that tuberactinomycin B is identical with the known antibiotic viomycin.[3] Although several structures for viomycin have been proposed[4~6] and recently BYCROFT *et al.* presented the formula of Fig. 2[7], these structures differ from our proposed structure for tuberactinomycin B. The following data were established conclusively the structure of tuberactinomycin B or viomycin.

When tuberactinomycin B was hydrolyzed with 1 N HCl at 100°C for 24 hours, a dipeptide was obtained by column chromatography of Dowex 50 W×2. Hydrolysis of the dipeptide after 2,4-dinitrophenylation gave N$^{\beta}$-2,4-dinitrophenyl-α, β-diaminopropionic acid and serine. This dipeptide is a diketopiperazine, *i.e.* cyclo-(α,β-diaminopropionylseryl) from the above experiments and from comparison with authentic synthesized diketopiperazine by thin-layer chromatography and paper electrophoresis.

Formation of this diketopiperazine can be explained by our structure, but not by BYCROFT's. The same diketopiperazine was also obtained from the partial hydrolyzates of tuberactinomycins A, N and O under similar reaction conditions.

The isolation of the diketopiperazine from the four tuberactinomycins is important for the determination of the amino acid sequence. We reported that the α-amino group of the α,β-diaminopropionic acid residue was linked to γ-hydroxy-β-lysine in tuberactinomycins A and N and to β-lysine in tuberactinomycins

Fig. 1. Chemical structure of tuberactinomycins.



	Tuberactinomycins			
	A	B	N	O
R_1	OH	H	OH	H
R_2	OH	OH	H	H

Tuberactinomycin B=Viomycin

Fig. 2. Structure by BYCROFT *et al.* for viomycin.

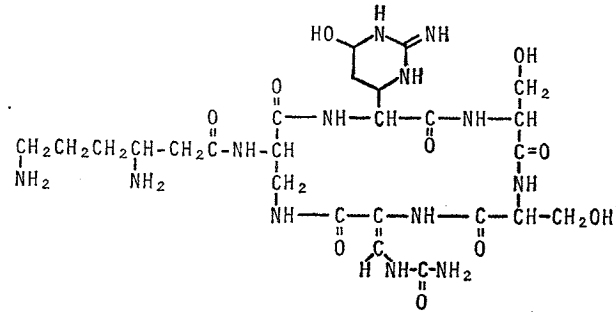


Table 1. Amino acid compositions of tuberactinomycins

Tuber-actino-mycins	Molecular formula	Ser	Dpr	Uda	Tbp	Cpd	γ-Hy-β-Lys	β-Lys
A	$C_{25}H_{43}N_{13}O_{11}$	2	1	1	1	—	1	—
B	$C_{25}H_{43}N_{13}O_{10}$	2	1	1	1	—	—	1
N	$C_{25}H_{43}N_{13}O_{10}$	2	1	1	—	1	1	—
O	$C_{25}H_{43}N_{13}O_{9}$	2	1	1	—	1	—	1

Ser : L-Serine. Dpr : L-α,β-Diaminopropionic acid. Tbd : L-Tuberactidine. Cpd : L-Capreomycidine. γ-Hy-β-Lys : γ-Hydroxy-L-β-lysine. β-Lys : L-β-Lysine. Uda : 3-Ureidodehydroalanine.

O and B (viomycin).[2] Therefore, the diketopiperazine must originate from the α,β-diaminopropionylseryl moiety common to the four peptides, but not from seryl-α, β-diaminopropionyl.

When the pure diketopiperazine was further treated with 1 N HCl at 100°C for 6 hours, it was converted to seryl-α,β-diaminopropionic acid exclusively without formation of α,β-diaminopropionylserine, whereas hydrolysis of the diketopiperazine with conc. HCl at room temperature gave both dipeptides. Ease of formation of seryldiaminopropionic acid under such mild condition by the rearrangement of amino acid sequence through the diketopiperazine may provide one explanation for the seryldiaminopropionyl sequence in the other proposed structure.[6] Thus, the amino acid sequence is the same for all tuberactinomycins including viomycin and the correct structure of viomycin is as shown in Fig. 1.

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