RELATIONSHIPS BETWEEN ANTIMICROBIAL ACTIVITIES AND CHEMICALLY REACTIVE FUNCTIONS IN VIOMYCIN

Sir:

Recent structural studies[1,2] on antibiotics of the viomycin series have led to two incompatible conclusions. As illustrated in Fig. 1, YOSHIOKA *et al.*[1] speculated formula I for viomycin by extending the result obtained by X-ray crystalographic analysis of tuberactinomycin O while, alomst at the same time, BYCROFT *et al.*[2] presented formula II from their degradative studies. Independent from these investigations, our chemical works on the primary structure of viomycin*, on one hand, resulted that its structure is to be formulated as I. On the other, these studies have provided us with a number of chemically modified derivatives of the antibiotic, especially the ones in which a specific functional group received modification in a specific manner.

Until now, our knowledge on structure-activity relationship of this antibiotic still remained meager, due to the lack of the systematic studies on this problem. Therefore, it is expected that investigations of individual activities of these compounds would supply valuable information to our limited knowledge on structure-activity relationship of this antibiotic.

Since viomycin possesses four chemically reactive functions as seen from Fig. 1, the derivatives in hand were classified into four groups: group A in which free amino groups of β-lysine terminus were blocked; group B in which free hydroxy function of serine residues were modified; group C in which the tuberactidine moiety was modified or transformed; and group D which had the transformed chromophore residues. In addition, other antibiotics of the viomycin series such as tuberactinomycins A, N and O[1,3] or capreomycins IA and IB[4], grouped as E, were also useful for the purpose of this experiment.

In Fig. 1, chemical structures of the used compounds are summarized and observed antimicrobial activities are given in Table 1.

Tuberactinomycins, capreomycins and viomycin showed a similar degree of potency. Though they differ in their amino acids

Table 1. Antimicrobial spectra of antibiotics and their derivatives

		MIC (mcg/ml)*					
		B. subtilis N	*B. subtilis* K	*P. vulg.*	*E. coli*	*P. aerug.*	*M.* 607
A	AcVM	>400	>400	>400	>400	>400	>400
	PrVM	400	>400	>400	>400	>400	400
	TFAVM	100	400	>400	400	>400	100
B	DIPVM	6.2	25	50	100	200	1.6
C	MeVM	6.2	25	100	100	400	1.6
	EtVM	6.2	12.5	100	200	400	1.6
	2HVM	25	25	200	400	400	6.2
D	4HVM	12.5	25	200	100	400	3.1
	DUVM	0.8	3.1	200	50	200	3.1
E	VM	3.1	12.5	25	50	100	1.6
	TUM A	3.1	12.5	25	50	100	3.1
	TUM N	1.6	12.5	25	50	200	1.6
	TUM O	3.1	12.5	25	50	200	1.6
	CPM IA	6.2	25	25	50	>100	3.1
	CPM IB	6.2	25	25	50	>100	3.1

* The MIC values are in mcg/ml and were determined by the two-fold tube dilution method.
B. subtilis N: *Bacillus subtilis* NRRL 3014. *B. subtilis* K: *B. subtilis* K-02.
P. vulg.: *Proteus vulgaris* OX-19. *E. coli*: *Escherichia coli* NIHJ.
P. aerug.: *Pseudomonas aeruginosa* Tsuchiiima. *M.* 607: *Mycobacterium* sp. 607.

* The details will be published.

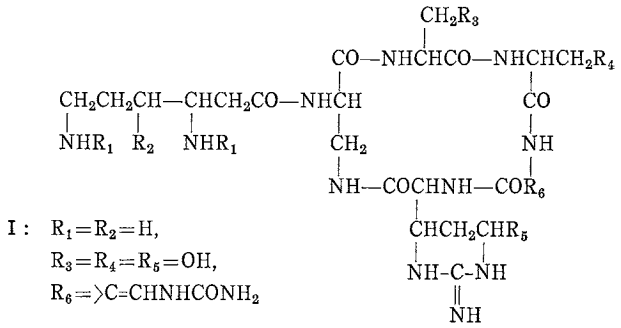
composition, the sixteen membered ring structure is a characteristic common to all of them besides having the same chromophore group. Therefore either one or both of these two structural faces are expected to be essential for the activities.

Judging from observed biological activities, it was concluded that acylations of free amino groups of β-lysine residue nullified the activity of the mother molecule while modification or substitution of serine hydroxy residues had almost no influence. The hydroxy function of tuberactidine moiety could be removed or alkylated without resulting in any significant change of the activity, suggesting that this function is not important. However, intactness of the six membered ring on tuberactidine residue seemed to be necessary for full expression of biological activity, since 2HVM in which the ring was reductically opened showed only less than one fourth of the potency of the original antibiotic.

The unexpected but rather interesting observations were made by assay of the derivatives grouped as D.

On the contrary to the above described expectation that the chromophore group might be indispensable, 4HVM in which the group was destructively hydrogenated to alanine with loss of urea component still maintained half to one fourth potency of the starting material and DUVM possessed rather stronger activities.

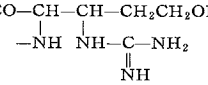
Fig. 1. Chemical structures of antibiotics and their derivatives



I: $R_1=R_2=H$, $R_3=R_4=R_5=OH$, $R_6=>C=CHNHCONH_2$

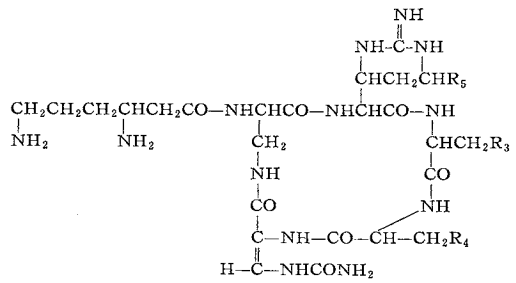
Group	peptide	R_1	R_2	R_3	R_4	R_5	R_6
A	AcVM PrVM TFAVM	CH_3CO C_2H_5CO CF_3CO	H	OH	OH	OH	$>C=CHNHCONH_2$
B	DIPVM	H	H	DIP	DIP	OH	$>C=CHNHCONH_2$
C	MeVM EtVM 2HVM	H	H	OH	OH	OCH_3 OC_2H_5 2HV	$>C=CHNHCONH_2$
D	4HVM DUVM	H	H	OH	OH	OH	$>CH-CH_3$ $>CH=CHOH$
E	VM	H	H	OH	OH	OH	$>C=CHNHCONH_2$
	TUM A		OH	OH	OH	OH	
	TUM N		OH	OH	OH	H	
	TUM O		H	OH	OH	H	
	CPM IA		H	OH	NH_2	H	
	CPM IB		H	H	NH_2	H	

Abbreviations; AcVM: acetylviomycin[5], PrVM: propionylviomycin[5], TFAVM: trifluoraocetylviomycin**, DIPVM: diisopropylphosphate ester of viomycin**, MeVM: methylviomycin[6], EtVM: ethylviomycin[6], DUVM: desureaviomycin[2], VM: viomycin, TUM: tuberactinomycin, CPM: capreomycin***. DIP=-OPO(OCHMe$_2$)$_2$, 2HV: dihydroviomycidine residue which chemical structure was determined as follows[7];



** Unpublished data.

*** The unified sequential structures **II**, **III** and **IV** for viomycin and capreomycins IA and IB were proposed by BYCROFT *et al.*[4] Since our degradative studies had performed with viomycin and not with capreomycins, amino acid sequences of these antibiotics should be formulated as **III** and **IV**.



II: $R_3=R_4=R_5=OH$
III: $R_3=OH$, $R_4=NH_2$, $R_5=H$
IV: $R_3=R_5=H$, $R_4=NH_2$

Explanations for this unexpected potency are awaiting further elucidation.

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