SYNTHESIS OF 5''-DEOXYLIVIDOMYCIN B

Sir:

Lividomycin B[1,2,3] is synonymous with 3'-deoxyparomomycin I and, therefore, the difference in antibacterial activity between paromomycin I and lividomycin B may be ascribed to the absence of the 3'-hydroxyl group in lividomycin B. As seen in Table 1, lividomycin B is active against *Pseudomonas aeruginosa* A 3 and *Escherichia coli* JR 66/W 677[4], whereas paromomycin shows no activity for these strains. However, lividomycin-B shows no activity against *E. coli* K 12-ML 1629 and K 12-ML 1630 carrying R factor, which is sensitive to 3'-deoxykanamycin, 3', 4'-dideoxykanamycin B and 3',4'-dideoxyneamine. Recently, KONDO *et al.*[5] found that the lividomycin A is inactivated by *E. coli* K 12-ML 1410 R 81 and *P. aeruginosa* TI-13 by phosphorylation of the 5''-hydroxyl group. Therefore, removal of the 5''-hydroxyl group of lividomycin B was undertaken.

Lividomycin B was treated with bezyloxycarbonyl chloride in methanol to give penta-N-benzyloxycarbonyllividomycin B (**1**) [yield, 92 %, $[\alpha]_D^{18}+40°$ (*c* 1.1, $CHCl_3$)], which was allowed to react with benzaldehyde dimethyl acetal in dimethyl formamide (DMF) in the presence of *p*-toluenesulfonic acid at 30°C under reduced pressure to give 4',6'-O-benzylidene-penta-N-benzyloxycarbonyllividomycin B (**2**), $[\alpha]_D^{18}+47°$ (*c* 0.85, $CHCl_3$) in a yield of 70 %. Found: C 61.59, H 5.77, N 5.11 %; Calcd. for $C_{70}H_{79}N_5O_{23}$: C 61.89, H 5.86, N 5.16 %. Selective tosylation of **2** with tosyl chloride in pyridine gave the corresponding 5''-O-tosyl derivative (**3**), $[\alpha]_D^{18}+24.5°$ (*c* 0.86, $CHCl_3$) in a yield of 60 %. NMR (in $CDCl_3$): τ 7.69 (3 H, s, $TsCH_3$). Found: C 61.05, H 5.43, N 4.68, S 2.25 %; Calcd. for $C_{77}H_{85}N_5O_{25}S$: C 61.14, H 5.66, N 4.62, S 2.12 %. Displacement of the tosyloxy group with iodine atom was performed with sodium iodide in DMF at 95°C for 2 hours to give the iodo compound $[\alpha]_D^{18}+39.4°$ (*c* 1, $CHCl_3$) in a yield of 94 %. Found: C 57.12, H 5.21, N 4.82, I 8.78 %; Calcd. for $C_{70}H_{78}N_5O_{22}I$: C 57.26, H 5.36, N 4.77, I 8.65 %. Reduction of **4** with RANEY nickel and hydrogen in the presence of triethylamine gave the corresponding 5''-deoxy derivative (**5**), $[\alpha]_D^{18}+33.3°$ (*c* 0.9,

Table 1. Antibacterial spectra of 5''-deoxylividomycin B, lividomycin B and paromomycin

Test organisms*	Minimal inhibitory concentration (mcg/ml)		
	5''-Deoxy lividomycin B	Lividomycin B	Paromomycin
Staphylococcus aureus FDA 209 P	25	1.56	1.56
Sarcina lutea PCI 1001	12.5	1.56	1.56
Bacillus subtilis NRRL B-558	0.78	<0.39	0.39
Klebsiella pneumoniae PCI 602	50	1.56	1.56
Salmonella typhosa T-63	6.25	<0.39	0.39
Escherichia coli NIHJ	100	3.12	3.12
〃 K-12	50	1.56	1.56
〃 K-12 ML 1629	100	>100	>100
〃 K-12 ML 1630	100	>100	>100
〃 K-12 ML 1410	50	6.25	3.12
〃 LA 290 R 55	100	3.12	3.12
〃 W 677	50	3.12	3.12
〃 JR 66/W 677	>100	6.25	>100
Pseudomonas aeruginosa A 3	>100	6.25	100
〃 No. 12	>100	25	100
〃 GN 315	>100	50	>100
〃 TI-13	>100	50	>100
〃 99	>100	100	>100
Proteus retttgeri GN 311	50	1.56	3.12
〃 GN 466	100	3.12	6.25
Mycobacterium smegmatis ATCC 607**	50	<0.39	0.78

* Agar dilution streak method (nutrient agar, 37°C, 18 hours)
** 48 hours

$CHCl_3$) in a yield of 60 %. Found: C 62.37, H 5.75, N 5.29 %; Calcd. for $C_{70}H_{79}N_5O_{22}$: C 62.63, H 5.93, N 5.22 %. Hydrogenation of **5** with palladium black and hydrogen in aqueous dioxane removed all protecting groups to give a crude product, which was purified by a column of CM-Sephadex C-25 with 0.12 N ammonia, yield 64 %, $[\alpha]_D^{20}$ + 56.6° (*c* 1, H_2O); NMR (in D_2O): τ 8.61 (3H, d, CH-C$\underline{H}_3$). On a paper-chromatogram with 1-butanol – pyridine – water – acetic acid (6 : 4 : 3 : 1) it gave $Rf_{lividomycin\,B}$ 1.1. Found: C 45.92, H 7.81, N 11.42 %; Calcd. for $C_{23}H_{45}N_5O_{12}\cdot H_2O$: C 45.91, H 7.87, N 11.66 %.

As seen in Table 1, the synthetic 5''-deoxylividomycin B shows markedly decreased antibacterial activity when compared with the parent antibiotic, but it shows almost equal activity (MIC, 100 mcg/ml) against several strains of *E. coli*, suggesting that lividomycin B is inactivated by *E. coli* K 12-ML 1629 and K 12-ML 1630 by modifying its 5''-hydroxyl group. At the same time, 5''-hydroxyl group is considered to be requisite for high antibacterial activity of lividomycin B and its derivatives.

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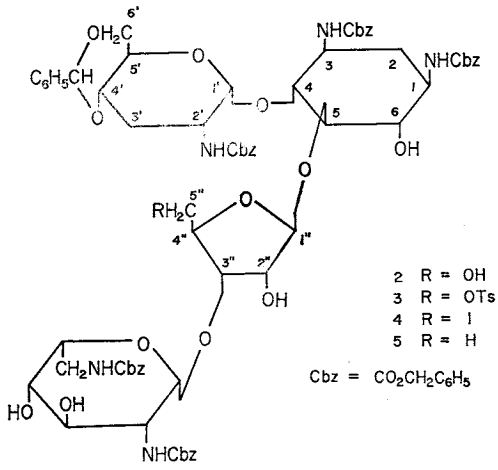

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