SYNTHESES OF 6′-AMINO-6′-DEOXYLIVIDOMYCIN B AND 6′-DEOXY-6′-METHYLAMINO- AND 6′-DEOXY-6′-(2-HYDROXYETHYLAMINO)-LIVIDOMYCIN B

Sir:

In this paper we report the syntheses of 6′-amino-6′-deoxylividomycin B, that is, 3′-deoxyneomycin B, and 6′-deoxy-6′-methylamino- and 6′-deoxy-6′-(2-hydroxyethylamino)-lividomycin B.

Paromamine[1] and 3′-deoxyparomamine[2] which is a structural component of lividomycins have markedly lower antibacterial activity than neamine and 3′,4′-dideoxyneamine[3]. The lower activity of the former compounds was thought to be due to the lack of 6′-amino group. 3′,4′-Dideoxykanamycin B[4] and 3′-deoxykanamycin B[5] (tobramycin) are active against resistant *Staphylococci* and resistant Gram-negative organisms including *Pseudomonas aeruginosa*, against which kanamycin B is inactive. Their strong activity against these resistant bacteria can be ascribed to the absence of the 3′-hydroxyl group, and their strong general antibacterial activity to the presence of the 6′-amino group. Comparison[6] of the antibacterial activity of 3′-deoxyribostamycin and 3′,4′-dideoxyribostamycin indicates that 3′-dehydroxylation gives a compound with stronger activity than 3′,4′-didehydroxylation in ribostamycin. Since lividomycins have neither 3′-hydroxyl nor 6′-amino groups, the replacement of its 6′-hydroxyl with an amino group was thought to give a derivative having enhanced activity against both resistant and sensitive organisms.

Acetylation of 4′,6′-O-benzylidene-1,3,2′,2‴,6‴-penta-N-benzyloxycarbonyl-lividomycin B[7] (**1**) in pyridine gave the 6,2″,5″,3‴,4‴-penta-O-acetyl derivative (**2**) quantitatively, $[\alpha]_D^{20}+21°$ (*c* 1, $CHCl_3$), which on treatment with a mixture of acetone-acetic acid-water (1:2:1) at 60°C, gave debenzylidenated product (**3**) in a yield of 94%, $[\alpha]_D^{14}+23°$ (*c* 1, $CHCl_3$). [Calcd. for $C_{73}H_{85}N_5O_{28}$: C 59.22, H 5.79, N 4.73; Found: C 59.18, H 5.67, N 4.80].

Treatment of **3** with tosyl chloride and cold pyridine (−10°C) gave the 6′-O-tosyl derivative (**4**) in 70% yield, $[\alpha]_D^{14}+29.5°$ (*c* 0.4, $CHCl_3$). [Calcd. for $C_{80}H_{91}N_5O_{30}S$: C 58.78, H 5.61, N 4.28, S 1.96; Found: C 58.95, H 5,41, N 4.34, S 2.11]. The presence of the 6′-O-tosyl group was proven by iodination of **4**, deacetylation, hydrogenation with Raney nickel and hydrogenolysis with palladium black, affording 6′-deoxylividomycin B (**5**), $[\alpha]_D^{16}+58°$ (*c* 1, H_2O); NMR (in D_2O): τ 8.77 (3 H d, *J* 6 Hz, $CHC\underline{H}_3$). [Calcd. for $C_{23}H_{45}N_5O_{12}\cdot H_2CO_3$: C 44.65, H

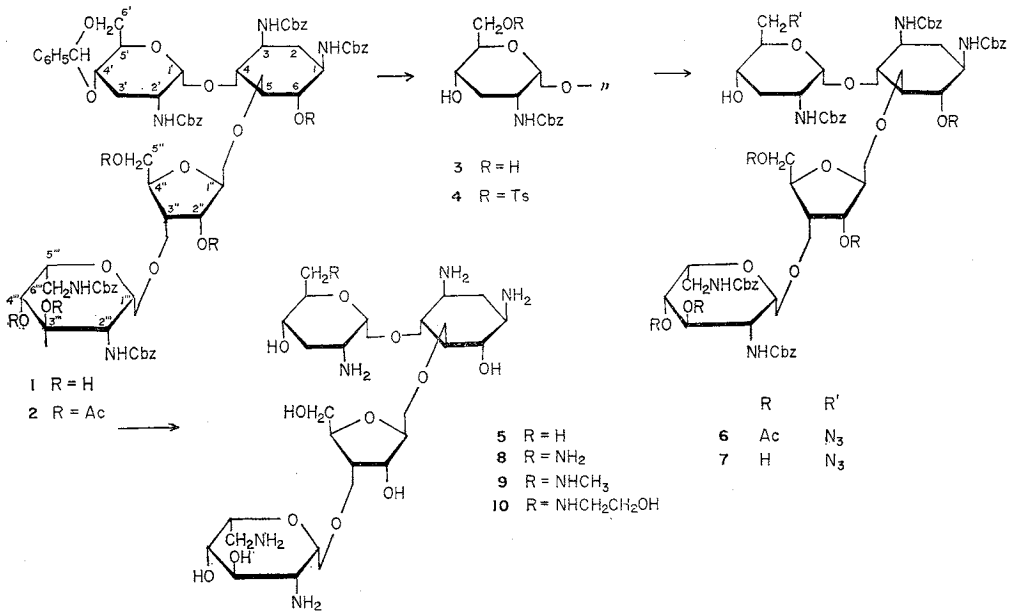

Table 1. Antibacterial spectra of 6′-amino-6′-deoxylividomycin B (ALVB), 6′-deoxy-6′-methylamino-lividomycin B (MALVB), 6′-deoxy-6′-(2-hydroxyethylamino)lividomycin B (HALVB), neomycin (NM) and lividomycin B (LVB)

Test organisms*	Minimal inhibitory concentration (mcg/ml)				
	ALVB	MALVB	HALVB	NM	LVB
Staphylococcus aureus FDA 209 P	<0.20	<0.20	0.39	0.39	1.56
Sarcina lutea PCI 1001	0.78	6.25	25	0.78	1.56
Bacillus subtilis NRRL B-558	<0.20	<0.20	<0.20	<0.20	<0.20
Klebsiella pneumoniae PCI 602	0.78	0.78	0.78	0.78	1.56
〃 type 22 # 3038	1.56	1.56	3.12	>100	6.25
Salmonella typhosa T-63	0.39	0.78	1.56	0.78	0.78
Escherichia coli NIHJ	0.78	3.12	3.12	1.56	3.12
〃 K-12	0.78	0.78	1.56	1.56	1.56
〃 〃 R-5	0.39	1.56	1.56	0.78	1.56
〃 〃 ML 1629	50	>100	>100	100	>100
〃 〃 ML 1630	50	>100	>100	>100	>100
〃 〃 ML 1410	1.56	3.12	3.12	6.25	6.25
〃 〃 〃 R 81	100	>100	>100	>100	>100
〃 〃 LA 290 R 55	1.56	1.56	1.56	0.78	3.12
〃 〃 〃 R 56	0.39	1.56	0.78	0.78	3.12
〃 〃 〃 R 64	0.78	0.78	1.56	0.39	3.12
〃 〃 C 600 R 135	0.78	0.78	1.56	0.78	3.12
〃 〃 W 677	0.78	0.78	1.56	0.78	3.12
〃 〃 JR 66/W 677	1.56	3.12	6.25	>100	6.25
〃 〃 J 5 R 11-2	25	100	>100	50	>100
Pseudomonas aeruginosa A 3	1.56	3.12	6.25	25	6.25
〃 No. 12	0.78	0.78	0.78	3.12	25
〃 GN 315	25	3.12	12.5	100	50
〃 TI-13-1	100	>100	>100	>100	>100
〃 99	1.56	25	25	50	100
Proteus rettgeri GN 311	25	25	50	50	1.56
〃 GN 466	3.12	12.5	6.25	3.12	3.12
Mycobacterium smegmatis ATCC 607**	<0.20	<0.20	<0.20	<0.20	0.39

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

7.34, N 10.85; Found: C 44.31, H 7.41, N 10.73].

Treatment of **4** with sodium azide in DMF gave the 6′-azido derivative (**6**) in 95% yield, $[\alpha]_D^{20}$+27.5° (*c* 1, $CHCl_3$); ir 2105 cm^{-1} (N_3). [Calcd. for $C_{73}H_{84}N_8O_{27}$: C 58.24, H 5.62, N 7.44; Found: C 58.10, H 5.70, N 7.41]. Compound **6** was treated with 5% methanolic ammonia to give the deacetylated product (**7**) quantitatively, $[\alpha]_D^{14}$+51° (*c* 1, $CHCl_3$). [Calcd. for $C_{63}H_{74}N_8O_{22}$: C 58.42, H 5.76, N 8.65; Found: C 58.33, H 5.93, N 8.76]. Hydrogenation with palladium black produced the 6′-amino group and cleaved the benzyloxycarbonyl groups to give the final product, which was purified by chromatography on CM-Sephadex C-25 (NH_4^+ form) with ammonia (0.1~0.25 N). 6′-Amino-6′-deoxylividomycin B (**8**) was obtained as the monocarbonate in a yield of 71%. $[\alpha]_D^{15}$+52° (*c* 1, H_2O), $Rf_{\text{lividomycin B}}$ 0.5 (ppc with 1-butanol-pyridine-water-acetic acid (6:4:3:1)). [Calcd. for $C_{23}H_{46}N_6O_{12}\cdot H_2CO_3$: C 43.63, H 7.32, N 12.72; Found: C 43.40, H 7.44, N 13.02].

Treatment of **4** with 30% methanolic methylamine at 50°C for 6 hours followed by hydrogenolysis with palladium black gave 6′-deoxy-6′-methylaminolividomycin B (**9**) in 47%

yield from **4**, $[\alpha]_D^{20}+60.5°$ (*c* 1, H_2O); NMR (in D_2O): τ 7.23 (3 H s, NCH_3). [Calcd. for $C_{24}H_{48}N_6O_{12}\cdot H_2CO_3$: C 44.50, H 7.46, N 12.46; Found: C 44.68, H 7.48, N 12.63]. Similar treatment of **4** with ethanolamine gave 6′-deoxy-6′-(2-hydroxyethylamino) lividomycin B (**10**), $[\alpha]_D+63.4°$ (*c* 1, H_2O). [Calcd. for $C_{25}H_{50}N_6O_{13}\cdot H_2O$: C 45.45, H 7.93, N 12.72; Found: C 45.34, H 7.83, N 12.55].

The synthetic 6′-amino-6′-deoxylividomycin B (**8**) exhibited markedly enhanced antibacterial activity against both sensitive and resistant bacteria and *Pseudomonas aeruginosa* (Table 1). Strain TI-13-1 of *Pseudomonas aeruginosa*, however, was resistant to this compound probably because this strain produces an enzyme which phosphorylates[8] the 5″-hydroxyl group of lividomycin A.

Modification of the 6′-hydroxyl group of lividomycin B with the methylamino[9] or 2-hydroxyethylamino group gave compounds effective against *Pseudomonas aeruginosa* GN 315. This strain is resistant to kanamycins and neomycins and has been reported[10] to produce an enzyme which acetylates the 6′-amino group. *Pseudomonas aeruginosa* 99[11], which acetylates the 3-amino group of gentamicins, was sensitive to 6′-amino-6′-deoxylividomycin B (**8**) but resistant to 6′-methylamino- and 6′-deoxy-6′-(2-hydroxyethylamino)lividomycin B (**9** and **10**, respectively).

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