SYNTHESIS OF 3′-DEOXYSELDOMYCIN 5

Sir:

The conversion of an equatorial 3′-hydroxyl group to the corresponding deoxy function in aminoglycoside antibiotics has been of current interest since the enzymic mechanism of inactivation of kanamycin by resistant bacteria had been clarified as 3′-O-phosphorylation. It has been shown by UMEZAWA's group that 3′-deoxykanamycin, designed rationally on this inactivation mechanism, exhibits strong antibacterial activity against these resistant strains[1]. Seldomycin 5 (**1**), a new aminoglycoside antibiotics found in our institute, has also an equatorial 3′-hydroxyl group and is inactivated by 3′-O-phosphorylation[2,3]. In a previous paper, we have reported that epimerization of the 3′-hydroxyl group in seldomycin 5 caused marked recovery of antibacterial activity against resistant strains[4]. The present communication describes the conversion of seldomycin 5 (**1**) into 3′-deoxyseldomycin 5 (**4**) and preliminary data on its biological activity.

Hexa-N-ethoxycarbonyl-3′-O-tosylseldomycin 5 (**2**), prepared as reported in a previous paper[4], was treated with sodium borohydride in DMSO[5], affording after usual work-up and chromatography (silica gel) pure hexa-N-ethoxycarbonyl-3′-deoxyseldomycin 5 (**3**) in 20.1% yield. m.p. 278~279°C, $[\alpha]_D^{25}$ +70.7° (*c* 0.382, DMF); Found: C 50.28, H 7.41, N 9.63, S 0.00%. Calcd. for $C_{36}H_{62}N_6O_{18}$: C 49.87, H 7.22, N 9.70, S 0.00%.

Removal of the ethoxycarbonyl groups of compound **3** with aq. potassium hydroxide-methanol followed by usual work-up and chromatography(Amberlite CG-50, ammonium cycle) gave 3′-deoxyseldomycin 5 free base (**4**) in a high yield as white powders. m.p. 180~210°C, $[\alpha]_D^{25}$ +105° (*c* 0.564, water); MW 434.2930 (high resolution mass spectrum): *m/e* 129, 145. Periodate uptake 1.0 mole/mole. PMR (D_2O): τ 4.93 (1H, d, J=4 Hz, H-1′), 5.04 (1H, d, J=3 Hz, H-1″), 7.9~9.0 (6H, m, H-3′, H-4′, H-2). Found: C 47.51, H 8.43, N 18.16%. Calcd. for $C_{18}H_{38}N_6O_6 \cdot \frac{1}{2}H_2CO_3$: C 47.72, H 8.46, N 18.05%.

The clear evidence that deoxygenation occurred at 3′-position and other functional groups in the molecule remained intact was obtained by comparison of the CMR spectrum of **4** with that of seldomycin 5 and the reported data of gentamicin

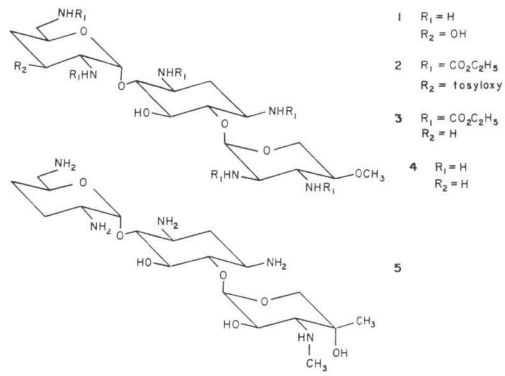

Table 1. CMR chemical shifts for 3′-deoxyseldomycin 5, seldomycin 5, and gentamicin C_{1a}*

	3′-Deoxy-seldomycin 5 (**4**)	Seldomycin 5 (**1**)[4]	Gentamicin C_{1a} (**5**)[6]
C-1′	102.2	101.9	102.2
C-2′	50.8	57.6	51.0
C-3′	27.0	69.0	27.1
C-4′	28.4	37.0	28.5
C-5′	71.5	70.8	71.5
C-6′	45.9	45.6	46.1
C-1	51.1	51.1	51.7
C-2	36.6	36.5	36.7
C-3	50.3	50.1	50.6
C-4	88.1	87.6	88.3
C-5	75.2	75.1	75.4
C-6	87.1	86.8	87.8
C-1″	100.1	99.9	101.3
C-2″	56.2	56.2	70.2
C-3″	54.8	54.8	64.4
C-4″	80.3	80.1	73.3
C-5″	60.8	60.8	68.7
OCH_3	58.7	58.8	—
NCH_3	—	—	38.0
CCH_3	—	—	23.0

* Measured in D_2O and reported in ppm from tetramethylsilane.

C_{1a} (**5**)[6] (Table 1). The latter compound and compound **4** have the common pseudo-disaccharide unit, gentamine C_{1a}.

The antibacterial activity of the compound **4** *in vitro* was shown in Table 2. It was found that 3′-deoxyseldomycin 5 (**4**) is, as expected, more potent than seldomycin 5 (**1**) against both gram-negative sensitive strains including *Pseudomonas aeruginosa* and those resistant strains which phosphorylate 3′-hydroxyl group of seldomycin 5 (**1**).

Table 2. The minimum inhibitory concentrations (mcg/ml) of 3′-deoxyseldomycin 5 (**4**) and seldomycin 5 (**1**).*

Strain	Inactivating enzyme**	1	4
Staphylococcus aureus Newman		1.56	0.78
Staphylococcus epidermidis		0.78	0.40
Micrococcus luteus ATCC 9341		3.12	6.25
Bacillus subtilis ATCC 6633		0.40	0.40
Escherichia coli NIHJ C-2		3.12	1.56
〃 R-5	APH(3′)-I, II	>100	3.12
〃 R-16	APH(3′)-I	>100	0.78
〃 R-17	AAC(6′)	1.56	1.56
〃 R-19	AAC(3)-I	50	>100
〃 R-20	APH(3′)-I	>100	1.56
Klebsiella pneumoniae #8045		1.56	0.78
Salmonella enteritidis G-14		12.5	12.5
Salmonella typhimurium E-9		3.12	1.56
Shigella sonnei ATCC 9290		6.25	3.12
Pseudomonas aeruginosa BMH#1		6.25	1.56
〃 BMH#10		3.12	0.78
〃 E-2		25	6.25
〃 R-5	APH(3′)-I, II	25	6.25
〃 R-9	AAC(6′)	>100	>100
〃 R-10	APH(3′)-I	>100	3.12
〃 R-12	AAC(3)-II	>100	>100
Serratia marcescens T-55		6.25	6.25
Providencia KY-3947		12.5	12.5
〃 164	AAC(2′)	>100	>100
Proteus vulgaris ATCC 6897		12.5	6.25
Proteus rettgeri KY-4288		6.25	1.56
Proteus morganii KY-4298		6.25	3.12

* Measured by agar dilution method at pH 7.2 specified by the Japan Society of Chemotherapy.

** For abbreviation of the inactivating enzymes, see MITSUHASHI, S.; L. ROSIVAL & V. KRCMERY: Drug inactivating enzymes and antibiotic resistance. p. 115, Springer-Verlag, Berlin, 1975

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