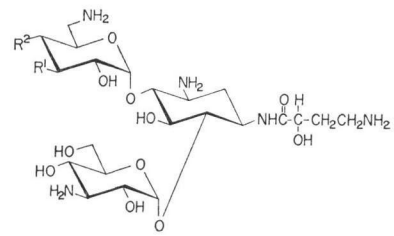
Communications to the editor

3′-DEOXYAMIKACIN AND 3′,4′-DIDEOXYAMIKACIN AND THEIR ANTIBACTERIAL ACTIVITIES

Sir:

As reported by UMEZAWA in 1968[1] and 1969[2], the 1-amino or the 3-amino group of the 2-deoxystreptamine moiety of kanamycin is involved in the binding of the antibiotic with 3′-O-phosphotransferases and the modification of one of these amino groups was suggested to produce derivatives active against resistant strains. In fact, butirosins[3] which contain a 1-N-(4-amino-2-hydroxybutyryl) group inhibit the growth of resistant strains and amikacin[4]; 1-N-(4-amino-2-hydroxybutyryl)kanamycin A shows a broad spectrum of activity against both sensitive and resistant strains. Therefore, we attempted the syntheses of 3′-deoxy and 3′,4′-dideoxy derivatives of amikacin, because we thought that such derivatives should show broader spectra against 3′-O-phosphotransferase-producing strains[5] than amikacin and be effective against 4′-O-adenylyltransferase-producing strains.[6,7] Moreover, this should give us additional information on the structure-activity relationships of kanamycin-like compounds.



	R^1	R^2
Amikacin (**1**)	OH	OH
3′-Deoxyamikacin (**2**)	H	OH
3′,4′-Dideoxyamikacin (**3**)	H	H
4′-Deoxyamikacin (**4**)	OH	H

3′-Deoxyamikacin (**2**) was prepared from 3′-deoxykanamycin A[8] by coupling the (*S*)-4-benzyloxycarbonylamino-2-hydroxybutyryl residue to the 1-amino group of 3′-deoxykanamycin A in the usual manner.[4] As will be reported in another paper[9], this coupling was also successfully accomplished by zinc chelation with Zn $(OAc)_2$ followed by regioselective N-trifluoroacetylation with ethyl trifluoroacetate. $[\alpha]_D^{25}+74°$ (*c* 0.4, water); Found: C, 42.68; H, 7.06; N, 10.53%. Calcd for $C_{22}H_{43}N_5O_{12}\cdot H_2CO_3\cdot H_2O$: C, 42.52; H, 7.29; N, 10.78%.

3′,4′-Dideoxyamikacin (**3**) was similarly prepared from 3′,4′-dideoxykanamycin A, $[\alpha]_D^{25}+80°$ (*c* 0.5, water); Found: C, 45.06; H, 7.08; N, 11.02%. Calcd for $C_{22}H_{42}N_5O_{11}\cdot H_2CO_3$: C, 44.95; H, 7.22; N, 11.40%. The starting 3′,4′-dideoxykanamycin A was prepared *via* 3′,4′-unsaturation of the corresponding 3′,4′-bisbenzylsulfonyloxy derivative of 6′-N-benzyloxycarbonyl-4″,6″-O-cyclohexylidene-5,2′-O-isopropylidene-2″-O-tetrahydropyranyl-1,3,3″-tri-N-tosylkanamycin A by treatment with sodium iodide-zinc powder in DMF in the usual manner[10], $[\alpha]_D^{25}+117°$ (*c* 1, water) as monocarbonate. Details of the synthesis of **2**, **3** and 3′,4′-dideoxykanamycin A will be described in the near future.

The antibacterial activity of **2** and **3** against several strains of bacteria of clinical origin is shown in Table 1 in comparison with those of amikacin (**1**) and 4′-deoxyamikacin[11] (**4**). In order to compare the activity of each compound, MIC values were transformed to the index values as shown in the first line of Table 1 because, if MIC values are used, the presence of one highly resistant strain produces a strong influence on the mean MIC value. Using the index values (1 for $\leqq$0.195 μg/ml, 2 for 0.39 μg/ml, 3 for 0.78 μg/ml . . .as shown in Table 1) the mean index (*c*) for each substance was calculated as follows:

$$c=\frac{\sum_{1\to 10}(\text{index})\times(\text{No. of strains with the index})}{\text{No. of all strains}}$$

This mean index value was transformed to a mean MIC value according to the following equation: mean MIC (μg/ml) $=d=(0.195/2)\cdot 2^c$. The strength of each substance was calculated from the value of d_0/d (d_0: *d* for amikacin). As shown in Table 1, **2** is found to be most active except against *Providencia*, against which **3** was most active. As reported by NAITO *et al.*[11], 4′-Deoxyamikacin (**4**) is much less active than **1**. Therefore, it can be concluded that the 3′-deoxygenation of amikacin increases the antibacterial activity and 4′-deoxygenation decreases the

Table 1. Antibacterial spectra of amikacin (**1**), 3′-deoxyamikacin (**2**), 3′,4′-dideoxyamikacin (**3**) and 4′-deoxyamikacin (**4**) for the strains of clinical origin.

	Index	1	2	3	4[a]	5	6[b]	7	8	9	10	*c*(*d*)	strength
	MIC (μg/ml)	≦0.195	0.39	0.78	1.56	3.12	6.25	12.5	25	50	≧100		
For *Klebsiella* (46 strains)*	**1**			13	15 (60)	7	7 (91)	4				4.43 (2.10)	1
	2		1	16	18 (76)	7	4 (100)					3.93 (1.49)	1.41
	3			16	13 (63)	7	9 (98)	1				4.26 (1.87)	1.12
	4				10 (22)	20	10 (87)	6				5.26 (3.74)	0.56
For *Serratia* (43 strains)	**1**			1		5	11 (40)	19	6		1	6.63 (9.66)	1
	2			1	3	8	23 (81)	7			1	5.86 (5.66)	1.71
	3			1	1	5	17 (56)	15	3	1		6.33 (7.84)	1.23
	4				1	1	6 (19)	11	18	5	1	7.47 (17.29)	0.56
For *Pyocyanique* (32 strains)	**1**					1	3 (13)	9	12	6	1	7.69 (20.13)	1
	2					1	3 (13)	9	15	3	1	7.59 (18.79)	1.07
	3					1	0 (3)	4	1	16	10	8.91 (46.90)	0.43
	4						1 (3)	2	4	17	8	8.91 (46.90)	0.43
For *Enterobacter* (28 strains)	**1**			2	7 (32)	11	3 (82)	3	1	1		5.18 (3.54)	1
	2			5	4 (32)	13	3 (89)	2	1			4.86 (2.83)	1.25
	3			3	10 (46)	5	6 (86)	2	1	1		5.04 (3.21)	1.10
	4				2 (7)	10	7 (68)	4	3	2		6.07 (6.55)	0.54
For *Proteus* (19 strains)	**1**					3	4 (37)	6	6			6.79 (10.79)	1
	2					5	5 (53)	5	4			6.42 (8.35)	1.29
	3				1	2	4 (37)	7	5			6.68 (10.00)	1.08
	4						3 (16)	4	8	4		7.68 (19.99)	0.54
For *Providencia* (16 strains)	**1**				1	1	4 (38)	10				6.44 (8.47)	1
	2				1	1	8 (63)	6				6.19 (7.12)	1.19
	3				1	2	8 (69)	5				6.06 (6.51)	1.30
	4					1	1 (13)	5	8	1		7.44 (16.93)	0.50
For *Citrobacter* (9 strains)	**1**				1	4	1	2		1		5.89 (5.78)	1
	2				2	3	2	1	1			5.56 (4.60)	1.26
	3				2	2	2	2	1			5.78 (5.36)	1.08
	4					2	2	3	1		1	6.78 (10.71)	0.54
For *E. coli* (8 strains)	**1**				2	3	3					5.13 (3.41)	1
	2			1	1	4	2					4.88 (2.87)	1.19
	3				2	2	3	1				5.38 (4.06)	0.84
	4					2	5	1				5.88 (5.74)	0.59

a: Ratio of cumulative number of strains (expressed as %) falling in the range of 0.195～1.56 μg/ml for the number of all strains.

b: for the range of 0.195～6.25 μg/ml.

* Number of susceptible strains.

activity.

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