SYNTHESIS OF 3′-DEOXYRIBOSTAMYCIN

Sir:

Recently we reported[1] the synthesis of 3′, 4′-dideoxyribostamycin. It was effective against resistant bacteria which produced kanamycin-neomycin phosphotransferase II[2]. In a previous paper on the synthesis of 3′-deoxykanamycin B[3] we reported a useful procedure for removing the 3-hydroxyl group from 2, 6-diamino-2, 6-dideoxy-D-glucose moiety of kanamycin B. In this paper we describe the synthesis of 3′-deoxyribostamycin by the same dehydroxylation method.

6, 5″-Di-O-acetyl-1, 3, 2′, 6′-tetra-N-benzyloxycarbonyl-2″, 3″-O-cyclohexylideneribostamycin[1] (**1**) (1 mol eq.) and tosyl chloride (5 mol eq.) were dissolved in pyridine and the solution was allowed to stand at 37°C overnight. On tlc (silica gel) with benzene-ethyl acetatae (5:1), the solution gave three spots, 0.46 (major, **2**), 0.57 (4′-O-tosyl isomer?) and 0.71 (3′, 4′-di-O-tosyl isomer?). Purification of the reaction mixture by column chromatography (silica gel) with benzene-ethyl acetate (5 : 2) gave the 3′-O-tosyl derivative (**2**) in 70% yield, mp 105~107°C, $[\alpha]_D^{25}$+4.9° (*c* 2, $CHCl_3$); NMR (in $CDCl_3$): τ 8.00 and 7.97 (each 3H s, Ac), 7.68 (3H s, Tos (CH_3)). [Calcd. for $C_{66}H_{76}N_4O_{22}S$: C 60.54, H 5.85, N 4.28, S 2.45; Found: C 60.52, H 5.85, N 4.19, S 2.68]. As by-products, the 4′-O-tosyl and di-O-tosyl compounds were obtained in yields of 10% and 3%, respectively. The tosyl group was replaced with iodine by the reaction with sodium iodide in DMF (100°C, 10 hr). Chromatography on silica gel with benzene-ethyl acetate (3 : 1) gave the 3′-iodo derivative (**3**) (36% yield), mp 103~106°C, $[\alpha]_D^{25}$+7° (*c* 1, $CHCl_3$); NMR (in $CDCl_3$): τ 7.96 and 7.93 (each 3H s, Ac). [Calcd. for $C_{59}H_{69}N_4O_{19}I$: C 56.01, H 5.50, N 4.43, I 10.03; Found: C 56.04, H 5.51, N 4.32, I 9.74]. Repeated hydrogenation of **3** with RANEY nickel in dioxane containing triethylamine gave the 3′-deoxy derivative (**4**) in a yield of 60%, mp 93~94.5°C, $[\alpha]_D^{25}$+1.4° (*c* 2, $CHCl_3$). [Calcd. for $C_{59}H_{70}N_4O_{19}$: C 62.20, H 6.19, N 4.92: Found: C 62.29, H 6.20, N 4.77]. Deacetylation of **4** with 10% methanolic ammonia gave the tetra-N-benzyloxycarbonyl-2″, 3″-O-cyclohexylidene derivative (**5**) quantitatively, mp 104~107°C (from benzene-n-hexane), $[\alpha]_D^{25}$ + 8.4° (*c* 3, $CHCl_3$). [Calcd. for $C_{55}H_{66}N_4O_{17}$: C 62.60, H 6.31, N 5.31; Found: C 62.39, H 6.35, N 5.10].

Compound **5** was successively treated with palladium black and hydrogen (50lbs/in²) in aqueous dioxane to remove the carbobenzyloxy groups, and with 1N hydrochloric acid to remove the cyclohexylidene group. The deblocked product was purified on a column of CM-Sephadex C-25 (NH_4^+ form) with ammonia (0~0.2N). 3′-Deoxyribostamycin (**6**) was obtained in 60% yield, mp 139~144°C (decomp.), $[\alpha]_D^{25}$+41° (*c* 1, H_2O); NMR (in D_2O at 100 MHz): τ 8.83 (1H q, *J* 13 Hz, H-2_{ax}), 8.40 (1H q, *J*~12 Hz, H-$3'_{ax}$), 8.2~7.9 (2H m, H-2_{eq}, H-$3'_{eq}$), 4.72

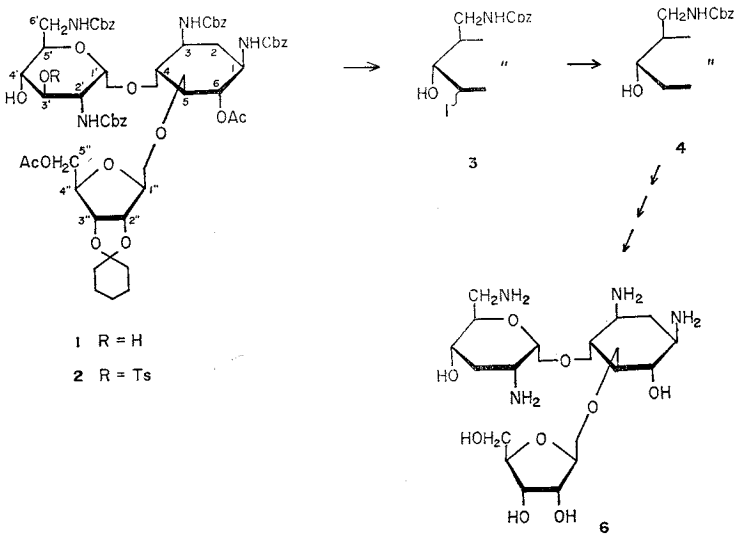

Table 1. Antibacterial spectra of 3′-deoxyribostamycin and 3′, 4′-dideoxyribostamycin

Test organisms*		Minimal inhibitory concentration (mcg/ml)	
		3′-Deoxyribostamycin	3′, 4′-Dideoxyribostamycin
Staphylococcus aureus	FDA 209 P	3.12	6.25
Sarcina lutea	PCI 1001	100	100
Bacillus subtilis	NRRL B-558	0.20	0.39
Klebsiella pneumoniae	PCI 602	1.56	6.25
〃	type 22 #3038	3.12	12.5
Salmonella typhosa	T-63	0.78	1.56
Escherichia coli	NIHJ	1.56	6.25
〃 K-12		0.78	3.12
〃 〃	R5	100	>100
〃 〃	ML 1629	100	>100
〃 〃	ML 1630	50	100
〃 〃	ML 1410	1.56	6.25
〃 〃	〃 R 81	>100	>100
〃 〃	LA 290 R 55	1.56	6.25
〃 〃	〃 R 56	1.56	3.12
〃 〃	〃 R 64	1.56	3.12
〃 〃	C 600 R 135	1.56	3.12
〃 〃	W 677	1.56	1.56
〃 〃	JR 66/W 677	6.25	12.5
〃 〃	J 5 R 11-2	50	100
Pseudomonas aeruginosa	A 3	3.12	12.5
〃	No. 12	6.25	12.5
〃	GN 315	>100	>100
〃	99	12.5	25
Proteus rettgeri	GN 311	6.25	12.5
〃	GN 466	3.12	6.25
Mycobacterium smegmatis	ATCC 607**	0.78	3.12

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

(2H m, 5Hz at half-height width, H-1′, H-1″). Upon irradiation at τ 7.11, the multiplet at τ 4.72 collapsed to slightly broadened singlet (2.5 Hz at half-height width), indicating that the signals of H-2′ is in the area of τ 7.11, and at the same time, the quartet at τ 8.40 (H-3′$_{ax}$) collapsed to a triplet. The NMR (in D_2O) of the tetrahydrochloride of **6**: τ 4.66 (1H d, J 1 Hz, H-1″), 4.14 (1H d, J 3.5 Hz, H-1′). [Calcd. for $C_{17}H_{34}N_4O_9 \cdot 2H_2O$: C 43.03, H 8.07, N 11.80; Found: C 43.59, H 8.07, N 11.75].

The synthetic 3′-deoxyribostamycin showed markedly enhanced antibacterial activity against sensitive and resistant bacteria (Table 1) as compared to 3′, 4′-dideoxyribostamycin.

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