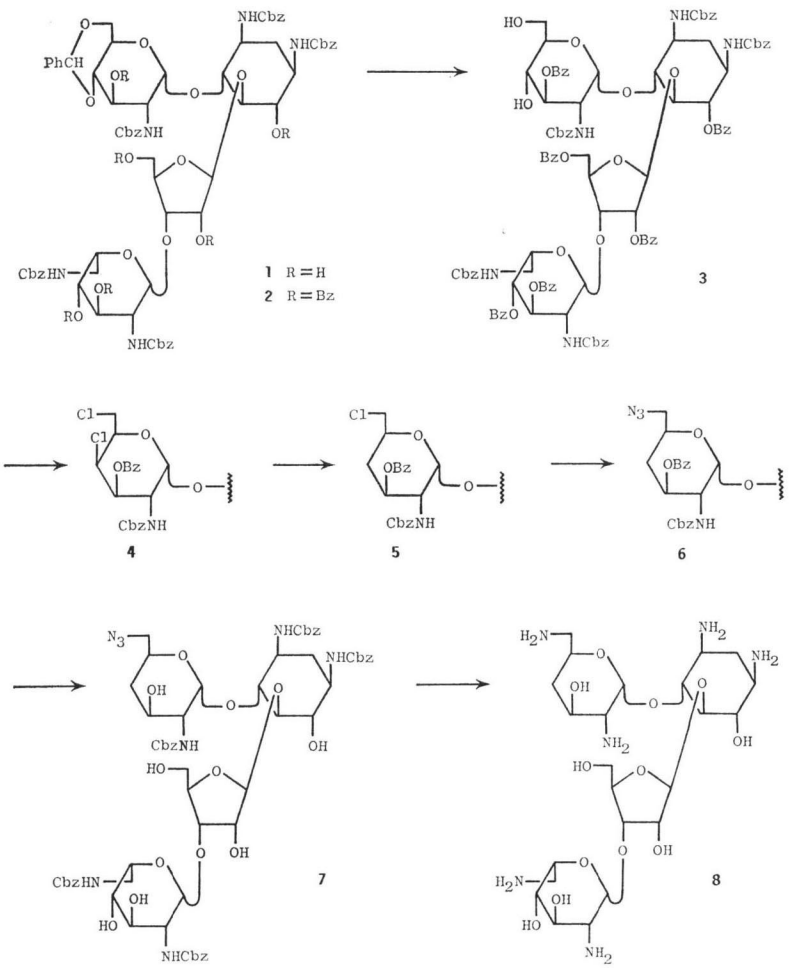
AMINOGLYCOSIDE ANTIBIOTICS 4′-DEOXYNEOMYCIN AND 4′-DEOXYPAROMAMINE

Sir:

In a continuation of our studies on the synthesis[1] and chemical modification[2] of aminoglycoside antibiotics, we report herein on the conversion of paromomycin into 4′-deoxyneomycin and of paromamine into 4′-deoxyparomamine. Our efforts in this direction were originally based on the reasonable premise that chemical modification in the immediate vicinity of the C–3′ hydroxyl group, a site which is phosphorylated by inactivating enzymes in bacteria[3], may in fact lead to impaired recognition, hence, improved antibacterial activity compared to the parent antibiotic. We were also encouraged by the finding of 4′-deoxybutirosins (Bu-1975 C_1 and C_2) from bacterial sources[4,5] and of their increased antipseudomonal activity. In keeping with previous trends among the 2-deoxystreptamine-containing aminoglycoside antibiotics of the ribostamycin type, these new analogs were also found to be less toxic than the gentamicin types[6]. 4′-Deoxygenated aminoglycosides with improved biological activity have since then been found from natural sources[7,8], and also prepared by semisynthesis from the kanamycins[9].

With the advent of several deoxygenation procedures, the main challenge in the conversion of paromomycin into 4′-deoxyneomycin resides in manipulating the available functional groups in such a way so as to expose the C–4′ and C–6′

Scheme 1.



positions for individual functional group transformations by methodology which is compatible with the substrate. The successful series of reactions are shown in Scheme 1.

The readily available 4′,6′-O-benzylidene acetal **1**[2] was benzoylated (BzCl, pyr., 60°C, 72 hours) to give the perbenzoate **2** in virtually quantitative yield. The amorphous solid was then treated with 90% aqueous AcOH (90°C, 6 hours) to give the diol **3** which was obtained as an amorphous solid (40% overall from paromomycin sulfate), after chromatography on silica gel. Treatment of **3** in pyridine solution with sulfuryl chloride[10,11]*, first at 0°C (1 hour) then at room temperature (48 hours) gave after usual workup an amorphous solid which was further purified on silica gel. The 4′,6′-dichloro derivative **4** was thus obtained as a colorless solid in 61% yield, $[\alpha]_D$+83.8°.** Selective reduction at the C-4′ position was readily accomplished with tributyltin hydride in the presence of AIBN[12] (85°C, 2 hours), to give the 6′-chloro-4′,6′-dideoxy derivative **5** as an amorphous solid (70% after column chromatography), $[\alpha]_D$+74.05°. Displacement with sodium azide in DMF (90°C, 48 hours, under N_2) and purification by column chromatography gave the 6′-azido derivative **6** as a colorless solid in 81% yield, $[\alpha]_D$+67.68°. Debenzoylation was achieved by treatment with methanolic NaOMe (pH ~8.5) with t.l.c. monitoring for 3 days. Chromatographic purification of the product so-obtained gave penta-N-benzyloxycarbonyl 6′-azido-4′,6′-dideoxyparomomycin **7** as an amorphous powder (72%); $[\alpha]_D$+41.5°. Finally, treatment of **7** with 10% Pd/C–H_2 in dioxane containing a little aqueous HCl resulted in the formation of the desired aminoglycoside as the hydrochloride salt. Conversion to the free base (Dowex-1, OH) followed by purification on CG-50 (NH_4^+) gave 4′-deoxyneomycin **8** as an amorphous white solid (85%); $[\alpha]_D$+36° (*c* 0.9, H_2O), Rf 0.4 in $CHCl_3$ - MeOH - NH_4OH (1 : 3 : 2); in the same system neomycin showed Rf 0.3. The structure of the product was confirmed by spectroscopic and mass spectral aids. Table 1 shows the antibacterial profile of **8** where it can be seen that in addition to maintaining the intrinsic activity of the neomycin-paromomycin group, it exhibits improved activity against various strains of *Escherichia coli* and *Pseudomonas aeruginosa* which are known to produce inactivating enzymes.

Table 1. Antibacterial activity of 4′-deoxyneomycin **8**.

	MIC mcg/ml		
	8	Neomycin B	Paromomycin
Staphylococcus aureus FDA 209 P	0.77	1.55	1.55
Escherichia coli K 12	3.12	6.25	12.5
E. coli K 12 R 112 (NPT I)	>200	>200	>200
E. coli K 12 R 118 (NPT II)	25	200	200
E. coli K 12 R 55(GNT)	3.12	6.25	12.5
Pseudomonas aeruginosa 9229	25	100	>100
P. aeruginosa 19660	25	50	>100
P. aeruginosa 4	12.5	25	>100
P. aeruginosa 5	25	50	>100
P. aeruginosa 6	12.5	25	>100
P. aeruginosa B	25	>100	>100
P. aeruginosa 47823	12.5	>100	>100
P. aeruginosa 53825	50	>100	>100
P. aeruginosa 53585	25	>100	>100
Proteus vulgaris	12.5	25	50
Proteus mirabilis 525	6.2	12.5	25
P. mirabilis V 15	12.5	25	25
Proteus sp. V 16	>100	>100	>100

In connection with our chlorination studies, the diol **3** was also converted into a 6′-monochloro derivative (−30°, 1.5 hours; 0°C, 10 minutes) (72.6%). Unfortunately, the derived 6′-chloro-6′-deoxy and 4′,6′-dichloro, 4′,6′-dideoxyparomomycin derivatives obtained by sequential debenzoylation and hydrogenolysis were much less active than the parent antibiotic.

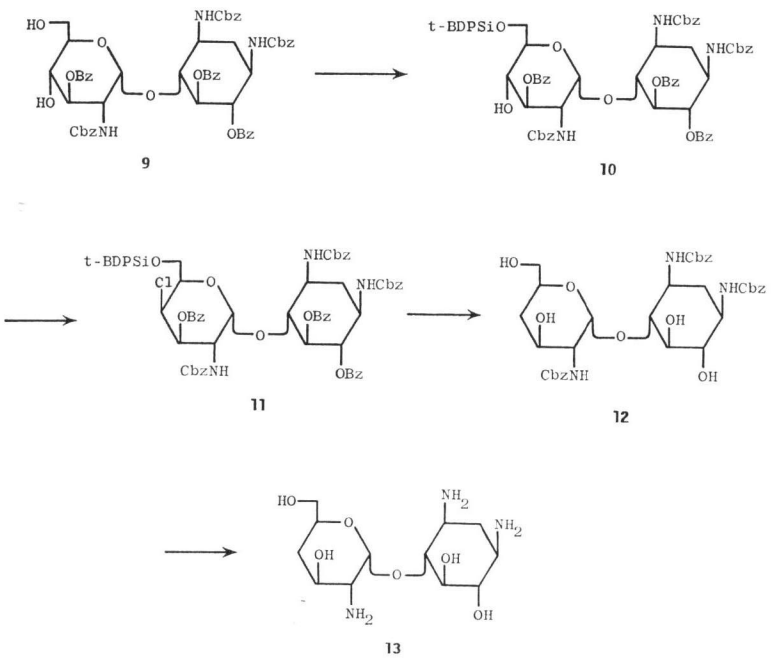
The sequence leading to the preparation of 4′-deoxyparomamine from paromamine follows a similar protocol as for the neomycin derivative. In addition, it illustrates the utility of the O-*t*-butyldiphenylsilyl group in the aminoglycosides series (Scheme 2).

Treatment of the readily available **9**[1] with *t*-butyldiphenylsilyl chloride as previously described[13] gave the 6′-ether **10**, $[\alpha]_D$+60.35°, as an amorphous solid (75% after chromatography). Chlorination as previously described gave the 4′-chloro derivative **12** as an amorphous solid (65%

* Efficient chlorination could also be effected in DMF in the presence of imidazole (84% yield). Details of this modification will be described elsewhere.

** New compounds gave correct microanalyses. Optical rotations were recorded in $CHCl_3$ unless otherwise mentioned.

Scheme 2.



overall), $[\alpha]_D$ +63.41° (pyridine). Finally, hydrogenolysis as described above, gave 4′-deoxyparomamine **13**, as the trihydrochloride salt (78%). Purification by chromatography on CG–50 (NH_4^+), gave the free base as a white powder (89%), mp ~190°C (dec.); $[\alpha]_D$ +106.2° (H_2O), which, as expected, exhibited improved antibacterial activity compared to paromamine.

We also had occasion to prepare 4′-chloro-4′-deoxyparomamine and 4′,6′-dichloro-4′,6′-dideoxyparomamine from paromamine by procedures similar to the ones described above. Unfortunately, these were inactive.

It is of interest that resistance in *Staphylococcus epidermidis* FK 109 is mediated by an enzyme that adenylates the 4′-hydroxyl group (also 4‴-) in a number of 2-deoxystreptamine-containing aminoglycoside antibiotics[14]. A similar enzyme has been isolated from *Staphylococcus aureus* that has developed resistance to these antibiotics[15] and such enzymes may be present in other strains as well. Deoxygenation at C–4′ may be a desirable functional modification in conjunction with other structural changes in the quest for aminoglycosides with broader antibacterial profiles. In this connection, compound **7** is a versatile precursor of 4′-deoxybutirosin and related aminoglycosides, by application of the oxidation-elimination sequence previously developed in this laboratory[2].

Acknowledgements

We thank Farmitalia - Carlo Erba, S.p.A. for generous financial assistance and for the antibacterial assays and microanalytical data.

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(Received January 30, 1980)

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