Communications to the editor

3′,4′-DIDEOXY-KANAMYCIN B ACTIVE AGAINST KANAMYCIN-RESISTANT *ESCHERICHIA COLI* AND *PSEUDOMONAS AERUGINOSA*

Sir:

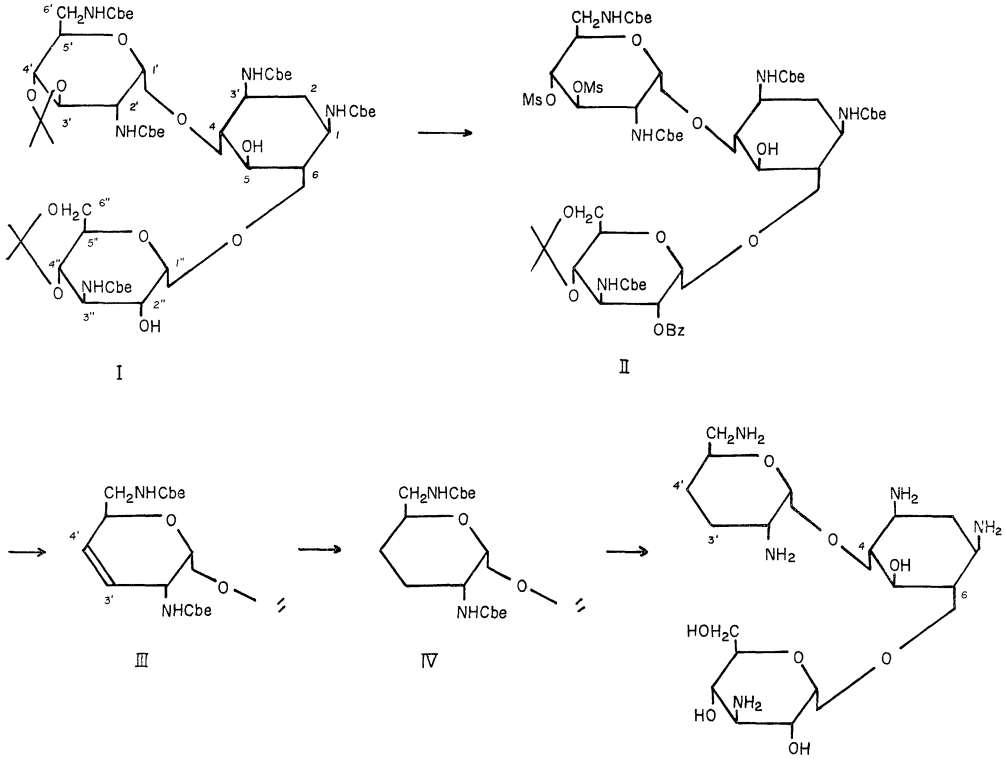
As described in the preceding communication[1], 3′-deoxykanamycin prepared by a synthetic method showed antibacterial activity against *E. coli* 1629, 1630 carrying R factor and *P. aeruginosa* for which kanamycin showed no activity. In this communication, the application of a similar principle to kanamycin B is described.

Since the preparation of 3′-deoxykanamycin B, which is the first candidate in the present project, by condensation of a suitable, protected 6-O-(3-amino-3-deoxy-α-D-glucopyranosyl)-2-deoxystreptamine derivative and a suitable, protected deoxyaminosugar derivative as described in the preceding communication[1] seemed tedious, direct transformation of kanamycin B was investigated. However, this transformation still requires a multi-step procedure. On the other hand, simultaneous removal of 3′ and 4′-hydroxyl groups through a 3′,4′-unsaturation derivative of kanamycin B is easier and studies on this product should give new information on the role of 4′-hydroxyl group. Thus the synthesis of 3′,4′-dideoxykanamycin B was attempted.

The amino group of kanamycin B were protected by carboethoxy chloride in aqueous acetone to give penta-N-carboethoxykanamycin B, m.p. 304~306°C, $[\alpha]_D^{22}$ +94° (*c* 0.3, DMF), which was more soluble in various organic solvents than the acetamido or benzamido derivatives of kanamycin B. The product was acetonated with 2,2-dimethoxy propane in DMF in the presence of *p*-toluenesulfonic acid and 3′,4′; 4″,6″-di-O-isopropylidene derivative (I) was obtained, m.p. 236~237°C, $[\alpha]_D^{20}$ +87° (*c* 1, DMF); NMR (in pyridine-d_5): τ 8.99 (3H t, $CH_2C\underline{H}_3$), 8.85 (12H t, $CH_2C\underline{H}_3$), 8.56 (12H broad singlet, Isop.). The 2″-hydroxyl group of compound I was benzoylated in the usual way without effect on the 5-hydroxyl group and the derivative, m.p. 205~209°C, $[\alpha]_D^{21}$ +114° (*c* 1, DMF), was deacetonated and again selectively monoacetonated to give the 2″-O-benzoyl-4″-6″-O-isopropylidene derivative, $[\alpha]_D^{21}$ +105° (*c* 1, DMF). Mesylation of the product with mesyl chloride in pyridine gave the corresponding 3′,4′-di-O-mesylated derivative (II), m.p. 198°C, $[\alpha]_D^{20}$ +107° (*c* 1.5, DMF); NMR (in pyridine-d_5): τ 6.60 and 6.45 (each 3H s, SO_2CH_3). 3′,4′-Unsaturation of compound II was performed by the method of TIPSON and COHEN[2] by the use of sodium iodide and zinc dust in DMF. The method was first applied to pyranoside-type sugars having *trans*-diequatorial sulfonic ester groups by HORTON *et al.*[3] and the method was successfully applied in the present synthesis. The product obtained, 2″-O-benzoyl-3′,4′-dideoxy-3′(4′)-eno-penta-N-ethoxycarbonyl-4″,6″-O-isopropylidene-kanamycin B (III), m.p. 282~284°C, $[\alpha]_D^{20}$ +36° (*c* 4, DMF) gave, in its NMR spectrum (in pyridine-d_5), a 2-proton, a slightly broadened singlet at τ 4.05 characteristic of 3′,4′-unsaturation compound (the chemical shifts of both

Table 1. Antibacterial spectra of 3′,4′-dideoxykanamycin B and kanamycin B

Test organisms*	Minimal inhibitory concentration (mcg/ml)	
	3′,4′-Dideoxykanamycin B	Kanamycin B
Staphylococcus aureus FDA 209P	0.78	0.78
Escherichia coli NIHJ	1.56	1.56
〃 K-12 CS-2	1.56	0.78
〃 K-12 ML 1629	1.56	>50
〃 K-12 ML 1630	3.12	>50
〃 K-12 ML 1410	1.56	0.78
Pseudomonas aeruginosa A 3	3.12	50
〃 No. 11	3.12	>50
〃 No. 12	6.25	50
〃 No. 39	6.25	>50
〃 No. 45	0.78	25
〃 No. 67	6.25	>50
Proteus rettgeri GN 311	12.5	3.12
〃 GN 466	3.12	1.50



Cbe: $CO_2C_2H_5$, Bz: COC_6H_5, Ms: SO_2CH_3

3′, 4′-Dideoxykanamycin B

protons are almost same and $J_{2',3'} \sim J_{4',5'}$ are ~0). Compound **III** was then catalytically hydrogenated to the corresponding dideoxy derivative (**IV**), $[\alpha]_D^{22}$ +93.5° (*c* 0.4, DMF), NMR (in pyridine-d_5): τ 7.8~8.5 (4H, CH_2CH_2), which, after deacetonation with 60 % acetic acid, was deacylated with barium hydroxide. The resulting product was purified by column chromatography with Amberlite IRC-50 and 0~0.5 N ammonia to give the final product, 3′, 4′-dideoxykanamycin B, $[\alpha]_D^{20}$ +132° (*c* 0.65, H_2O). The elemental analysis and hydrolysis with 6 N hydrochloric acid confirmed the structure of the product as expected. The synthesized 3′, 4′-dideoxykanamycin B showed antibacterial activity as strong as that of parent substance, kanamycin B, against bacteria tested and moreover showed activity against *E. coli* 1629, 1630 carrying R factor and *P. aeruginosa* against which kanamycin B showed no activity as shown in Table 1. This compound has as low toxicity as kanamycin B (LD_{50} 150 mg/kg mouse, iv).

This result and that reported in preceding communication[1] confirmed that the removal of the hydroxyl group, which may be phosphorylated by drug-resistant bacteria, yields compounds with activity against the resistant organisms.

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