The Total Synthesis of Kanamycin C

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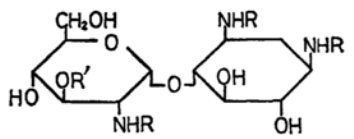
Kanamycin C[1] is a member of kanamycin congeners and composed of paromamine and 3-amino-3-deoxy-D-glucose. We wish to report a synthesis of this antibiotic. Since we have synthesized paromamine[2] (I), the combined achievements constitute the first total synthesis of kanamycin C (VIII).

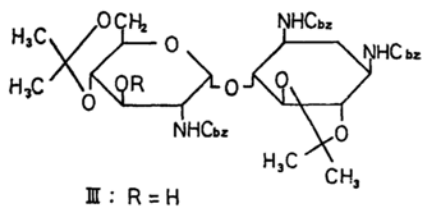
Tri-*N*-carbobenzoxyparomamine (II), mp 258°C (decomp.), $[\alpha]_D^{18}$ +64.5° (*c* 0.67, DMF), was treated with 2, 2-dimethoxypropane and *p*-toluenesulfonic acid in *N*, *N*-dimethylformamide (DMF) to give the diisopropylidene derivative(III). Benzylation of III with benzyl bromide in the presence of barium oxide and barium hydroxide in DMF gave IV, which, by deacetonation, gave V. When partially acetonated, V gave monoisopropylidene-monobenzyl derivative (VI); mp 239—241°C, $[\alpha]_D^{18}$ +75° (*c* 0.63, DMF).

The condensation of VI with 3-acetamido-2, 4, 6-tri-*O*-benzyl-3-deoxy-*α*-D-glucopyranosyl chloride[3] [mp 143—144°C (decomp.), $[\alpha]_D^{23}$ +78° (*c* 1.0, $CHCl_3$)] in a mixture of benzene-dioxane in the presence of mercuric cyanide and Drierite gave the condensation product. After removal of the all protecting groups, the resulting free base was dinitrophenylated and *O*-acetylated. The product was chromatographed on a silica-gel column with a solvent system (A): toluene-MEK (2 : 1), to afford yellow crystals of VII; 15% over-all yield from VI; mp 208—211°C (decomp.), $[\alpha]_D^{18}$ +285° (*c* 0.75, acetone).

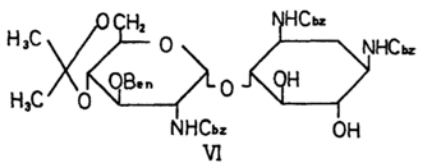
On the other hand, kanamycin C[1] was dinitrophenylated and acetylated to give hepta-*O*-acetyltetra-*N*-(2, 4-dinitrophenyl)-kanamycin C; mp 208—211°C (decomp.), $[\alpha]_D^{18}$ +299° (*c* 0.64, acetone). On TLC with a solvent system (A), the synthetic product VII and the above-mentioned derivative of natural kanamycin C showed identical mobilities andt heir IR spectra were superimposed. Hydrolysis of VII with methanolic ammonia followed by treatment with Dowex 1×2 (OH) gave a crude free base, which was purified by column-chromatography to give VIII; $[\alpha]_D^{18}$ +139° (*c* 0.50, water). The natural kanamycin C showed $[\alpha]_D^{18}$ +145° (*c* 0.58, water) [lit.,[1] $[\alpha]_D^{20}$ +126° (water)]. Paper chromatography and IR spectra showed that VIII was identical with the natural kanamycin C. The antibiotic spectra and minimal inhibitory concentrations of the synthetic product VIII against test organisms were in agreement with those of the natural kanamycin C.



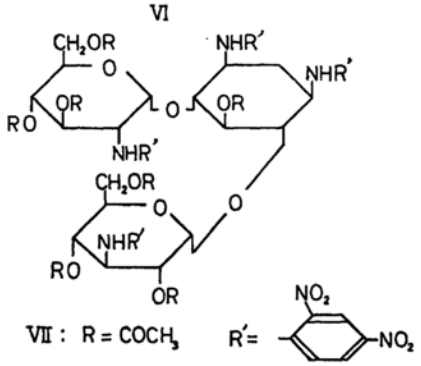
I : R, R' = H (Paromamine)
II : R = $COOCH_2C_6H_5$ R' = H
V : R = $COOCH_2C_6H_5$ R' = $CH_2C_6H_5$



III : R = H
IV : R = $CH_2C_6H_5$



VI



VII : R = $COCH_3$ R' =

VIII : R, R' = H (Kanamycin C)

1) K. Maeda, M. Ueda, K. Yagishita, S. Kawaji, S. Kondo, M. Murase, T. Takeuchi, Y. Okami and H. Umezawa, *J. Antibiotics*, **A10**, 228 (1957); J. W. Rothrock, R. T. Goegelman and F. J. Wolf, *Antibiotics Annual*, **1958/59**, 796; M. Murase, *J. Antibiotics*, **A14**, 367 (1961).

2) S. Umezawa and S. Kotō, This Bulletin, **39**, 2014 (1966); *J. Antibiotics*, **A19**, 88 (1966).

3) This compound have been reported by S. Umezawa *et al.* at the 20th Annual Meeting of the Chemical Society of Japan, Tokyo, March, 1967.